Measuring the Health and Development of School-age Zimbabwean Children

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Submitted in partial fulfilment of the requirements of the Degree of Doctor of Philosophy

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Joseph Piper

Date: 12th November 2023

Abstract

Health, growth and development during mid-childhood (from 5 to 14 years) are poorly characterised, and this period has been termed the 'missing middle'. This thesis describes the piloting and application of the School-Age Health, Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox to measure growth, cognitive and physical function amongst the SHINE cohort in rural Zimbabwe.

The SHINE cluster-randomised trial tested the effects of a household WASH intervention and/or infant and young child feeding (IYCF) on child stunting and anaemia at age 18 months in rural Zimbabwe. SHINE showed that IYCF modestly increased linear growth and reduced stunting by age 18 months, while WASH had no effects. The SAHARAN toolbox was used to measure 1000 HIV-unexposed children (250 in each intervention arm), and 275 HIV-exposed children within the SHINE cohort to evaluate long-term outcomes. Children were re-enrolled at age seven years to evaluate growth, body composition, cognitive and physical function.

Four main findings are presented from the SAHARAN toolbox measurements of this cohort. Firstly, child sex, growth and contemporary environmental conditions are associated with school-age physical and cognitive function at seven years. Secondly, early-life growth and baseline environmental conditions suggest the impact of early-life trajectories on multiple aspects of school-age growth, physical and cognitive function. Thirdly, the long-term impact of HIV-exposure in pregnancy is explored, which indicate reduced cognitive function, cardiovascular fitness and head circumference by age 7 years. Finally, associations with the SHINE trial early life interventions are explored, demonstrating that the SHINE early-life nutrition intervention has minimal impact by 7 years of age, except marginally stronger handgrip strength. The public health implications advocate that child interventions need to be earlier (including antenatal), broader (incorporating nurturing care), deeper (providing transformational WASH) and longer (supporting throughout childhood), as well as targeting particularly vulnerable groups such as children born HIV-free.

Acknowledgements

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Prof Andy Prendergast has been an exceptionally friendly and visionary mentor in supporting my steps within global health research, starting from when I was a foundation doctor, through my academic clinical fellowship (ACF) and throughout this fellowship. His boundless enthusiasm, ready wit, razor-sharp science and passion for nurturing initiative and independence is truly exemplary as both supervisor and friend. Andy remains an inspiring source of wisdom, good humour, encouragement and commitment throughout all the trials and tribulations of research. During the myriad challenges of research, his optimism, problem-solving, patience and belief in me has made this PhD immensely rewarding and enjoyable. I am extremely grateful for his care, commitment and approachability in supervising me at all stages. His cheery Whatsapp voice-notes during grant-writing seasons are always a joy. I am thankful also to Prof Jonathan Grigg who was my second supervisor and Prof Ian Sanderson for their unwavering support of this project. Prof Jonathan Wells has provided superb guidance and advice on growth and body composition. Dr Marko Kerac and Carlos Eternod-Grijalva helped immensely with physical function measurement and Prof Liz Allen with statistical input, including for the original WT grant proposal. Melissa Gladstone and Tamsen Rochat

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The Zvitambo Institute for Maternal Child Health and Research has been a second family in Zimbabwe. Everyone in the institute has been so welcoming and supportive. Their passion, professionalism and wisdom for research has been inspiring and I continue to learn so much from everyone there. On my first trip in 2015, Andy showed me the path to Zvitambo across the Monavale Vlei. Jean Humphrey's huge smile, encouragement and support set the tone to be involved at all levels; she also supported my ACF on body composition in the SHINE cohort which provided the foundations for this project. In the head office, Virginia Sauramba has provided endless support and encouragement with compliance, immigration, translations and other paperwork. Stephen Moyo has provided logistical support at all levels, along with the drivers particularly Clements, Lovemore and Shepherd. Phillipa, Tracy and Karen at the finance team have provided financial administrative support. Naume Tavengwa and Lisa Langhaug have provided helpful directorial support and insights. Kuda Mutasa has been instrumental in coordinating lab supplies and testing. Batsi Mutasa, Joice Tome, Rachel and the rest of the data team have also been key, particularly Joice for all her hard work on cleaning the data. Special mention should also go to Robert Ntozini, a fount of wisdom on statistics, the SHINE dataset and Zimbabwean life who has provide invaluable support and training on Stata programming. Similarly also to Bernard Chasekwa for all his help with statistics and Stata. Eddington Mpofu provided key database construction, where we also took our first steps in ODK together. Theo and Robert have also provided great server and electrical support despite a multitude of challenges.

For the field team, I would particularly like to thank Clever Mazhanga the SHINE project lead who has been instrumental in ensuring SHINE Follow-up happened and achieved its targets. His determination, initiative, insight, wisdom and enthusiasm continue to be truly inspiring. Likewise, Marian Mwapaura's work as field data officer has been exemplary and inspiring for her initiative, enthusiasm and attention to detail. Together with Gabriel Mbewe, their dedication has ensured the best outcomes for visit coordination, data collection and ongoing work with the community. Special thanks must also go to 'the manager' Dzie Chidhanguro, the field manager who continues to coordinate the hub with amazing leadership, insights and friendliness. Peter Maparanga has provided superb field logistics and Mai Bushe has kept the hub immaculate and fed me delicious Zimbabwean meals on numerous occasions.

A special thanks must go to the SHINE Follow-up team, particularly the data collectors and drivers, who have shown amazing determination, professionalism, dedication and cheerfulness in the face of multiple challenges. Each data point to provide the insight into rural children's growth and development included several hours of driving to a household, 4 hours of measurement and several hours driving back with the risks from breakdowns, rains and challenging roads. The first four data collectors who performed the pilot Gloria Mapako, Idah Mapurisa, Tsitsi Mashedze and Eunice Munyama all provided invaluable insights, professionalism and humour to show that the SAHARAN toolbox was feasible. The additional four data collectors Maria Kuona, Thombizodwa Mashiri, Kundai Sibanda, and Dzidzai Matemavi learnt and continued at this exceptional standard. Special thanks also to the intervention nurses Monica Tichagwa, Soneni Nyoni, Asinje Saidi, Manasa Mangwende who helped coordinate visits as well as performing consent and the caregiver questionnaire to get our visit schedule back on target after COVID disruption. Also to Tawanda and Lovemore as field drivers. I was also delighted to welcome Rudo and Mucha to join for the next phase of measurements.

I would like to personally thank all the members of the District Health executive (DHE), particularly Dr Nyachowe, the district medical officer (DMO). As DMO, Dr Nyachowe has provided fantastic support, invaluable scientific insights and wisdom into the myriad of challenges of field research. Together the DHE have guided us how best to work with the community and this study would have been impossible without them. I also thank the provincial medical office, district and provincial schools' inspector James Machimbirai and Ministry of Health and Child Care (MOHCC), particularly Handrea Njovo and Mary Muchekeza for their support. The Community engagement advisory board (CEAB)'s work is also much appreciated. Similarly, the community healthworkers have shown great dedication and organisation to coordinate SHINE Follow-up visits and community sensitisation. I would particularly like to thank Prof Helen Elsey and Prof Paula Griffiths for very helpful insights and suggestions for improving the thesis during the viva.

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Contribution

The work in this thesis has involved many researchers across Zimbabwe and the UK for the SHINE follow-up study. Below I have described my role in the research and the contributions of others.

SHINE Study

The original Sanitation, Hygiene Infant Nutrition Efficacy (SHINE) study was designed and led by principal investigator Prof Jean Humphrey, with the sponsor being Johns Hopkins University and registered as NCT01824940 and Medical Research Council of Zimbabwe (MRCZ/1675/A). The full trial design paper is available at https://pubmed.ncbi.nlm.nih.gov/26602296/ and primary outcome paper is here which lists the full SHINE trial team https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30374-7/fulltext

After the primary outcome was published, the PI then changed to Prof Andrew Prendergast and Zvitambo Institute became the trial sponsor. The SHINE follow-up (SFU) study was registered on with Pan-African Clinical Trials Register with number PACTR202201828512110 and MRCZ. The full SHINE Follow-up trial team are listed online in the Trial Design paper at https://wellcomeopenresearch.org/articles/8-306

Particular contributions are detailed here and by chapter. Robert Ntozini: Associate Director of Statistics, IT & Data Management, managed all data management and data analysis, with support from Bernard Chasekwa, Joice Tome and Batsi Mutasa. Virginia Sauramba coordinated compliance and ethical approvals with Lisa Langhaug. Naume Tavengwa coordinated the field team and liaison with the DHE, with assistance from Dzivaidzo Chidhanguro. Stephen Moyo and Lisa Langhaug managed logistics. Clever Mazhanga supported and managed the data collection nurses and fieldwork. Marian Mwapaura and Gabriel Mbewe were field data officers and managed field data collection. Eddington Mpofu supported ODK development, built and maintained the server. Andrew Prendergast directed all measurement, clinical and data collection aspects of the follow-up trial.

Chapter 1

Chapter 1 includes a narrative review examining stunting and the importance of school-age follow-up, as well as descriptions of the SHINE trial and HIV as an exposure. I performed this narrative review drawing on conversations with Andy Prendergast, Jonathan Wells and Carlos Eternod Grijalva.

Chapter 3

Chapter 3 details the development of the SAHARAN toolbox and methods within the SHINE follow-up trial which have been previously described in published papers. I designed the SAHARAN toolbox in collaboration with the experts described in the appendix and the chapter. I performed fieldwork with Clever Mazhanga and supervised data collection amongst four data collectors (Gloria Mapako, Idah Mapurisa, Tsitsi Mashedze and Eunice Munyama). I did the statistical analysis, in conversation with Robert Ntozini on how to present the results of the pilot. For the KABC-II adaptation, Elizabeth Allan suggested calculating the intra-class correlation coefficient, and Tamsen Rochat provided advice on ordering of the questions. Robert Ntozini assisted with the Tukey test. For the SHINE follow-up Trial design, myself, Andrew Prendergast, Robert Ntozini and Melanie Smuk all wrote the statistical analysis plan. Robert Ntozini and Melanie Smuk performed the sample size calculation.

The SAHARAN film available on youtube was filmed by Clever Mazhanga and myself. I then collected the clips and wrote an initial draft and commentary which was edited and approved by Andrew Prendergast, the SFU team and DHE. Lauren Wigmore (Video editor) then edited the clips together and added the music. This was reviewed and re-edited by Andrew Prendergast and then uploaded onto youtube. The SHINE Follow-up (SFU) team included:

Position	Name	Position	Name
Project Lead	Clever Mazhanga	Research Nurse	Manasa Mangwende
Field Data Officer	Marian Mwapaura	Field Hub Manager	Dzivaidzo Chidhanguro
Field Data Offcier	Gabriel Mbewe	Programmer	Eddington Mpofu
Data Collector	Gloria Mapako	Statistician / Data	Joice Tome
Data Collector	Idah Mapurisa	Data Manager	Batsirai Mutasa
Data Collector	Tsitsi Mashedze	Statistician	Bernard Chasekwa
Data Collector	Eunice Munyama	Statistician / IT	Robert Ntozini
Data Collector	Maria Kuona	Lab / testing support	Kuda Mutasa
Data Collector	Thombizodwa Mashiri	Compliance / translation	Virginia Sauramba
Data Collector	Kundai Sibanda	Compliance	Lisa Langhaug
Data Collector	Dzidzai Matemavi	Research management	Naume Tavengwa
Research Nurse	Monica Tichagwa	Field logistics	Peter Mapauranga
Research Nurse	Soneni Nyoni	Central logistics	Stephen Moyo
Research Nurse	Asinje Saidi	Reserve driver	Loyd Goremusandu
Driver	Lovemore Chingaona	Driver	Tawanda Mpofu

The SHINE Follow-up trial team

Chapter 4

Data cleaning was performed by Joice Tome and myself, using some do-files I had previously written for the pilot analysis. Joice Tome derived the CONSORT diagram. Robert Ntozini, Bernard Chasekwa, Andy Prendergast and myself derived the DAG and adjusted model. I performed the statistical analysis examining associations with sex, correlations between tests and contemporary growth. Robert Ntozini helped correct a Stata do-file which output the results from Generalised estimating equations to an excel sheet, which I then adapted for calculations throughout this thesis. I performed the principal components analysis and hierachical clustering with support and supervision from Bernard Chasekwa, Robert Ntozini and Melanie Smuk. Melanie Smuk and Robert Ntozini devised the LASSO-GEE method to explore contemporary exposures. Melanie Smuk performed the LASSO-GEE statistical analysis of contemporary environmental exposures and I interpreted it.

Chapter 5

Joice Tome, Batsi Mutasa and Robert Ntozini led on cleaning the baseline data. Joice Tome performed the comparison of baseline characteristics between those enrolled and not enrolled into SHINE Follow-up. Robert Ntozini, Andy Prendergast, Bernard Chasekwa and myself derived the DAG and adjusted model for early-life exposures. I performed the statistical analyses of early-life growth and catch-up growth on school-age outcomes, with support and supervision from Robert Ntozini and Bernard Chasekwa. Melanie Smuk performed the LASSO-GEE statistical analysis of baseline environmental exposures and I interpreted it.

Chapter 6

Joice Tome performed the comparison between CBHF and CHU. Robert Ntozini, Andy Prendergast and myself derived the DAG and adjusted model for HIV exposure for early-life and contemporary covariates. Robert Ntozini, Andy Prendergast, Bernard Chasekwa and myself derived the DAG's and adjusted models for HIV exposure for firstly early-life exposures and secondly contemporary exposures. I performed the statistical analysis comparing CBHF to CHU for all outcomes, and sub-analyses of child sex, with support and supervision from Robert Ntozini and Bernard Chasekwa.

Chapter 7

Joice Tome performed the comparison of the SFU cohort between intervention arms. Robert Ntozini, Andy Prendergast, Bernard Chasekwa and myself derived the DAG for the adjusted model. Robert Ntozini wrote the unblinding code and check for interaction and I checked it. Robert Ntozini performed the unblinding for unadjusted analysis. I performed the adjusted analysis and interpreted the results, with support from Robert Ntozini. I performed the sensitivity analyses, and also the detailed cognition and physical function subtests analysis.

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List of abbreviations

Abbreviation	Explanation
ACE	Adverse Child Experience
ART	Anti-retroviral therapy
CBHF	Children born HIV-free (children who are born from mothers with HIV and are HIV negative)
CHU	Children unexposed to HIV (i.e. born to mothers without HIV)
CHW	Community Health workers who work within the catchment area of the SHINE households, and are employed by the Zimbabwean Ministry of Health and Child Care.
CI	Confidence interval, usually set at 95%, which refers to a range of values where there is a 95% chance of the value being within this range.
CPRS	Child Parent Relationship Scale, a measure of nurturing
DAG	Directed Acyclic Graph
DC	Data Collector
EPDS	Edinburgh Postnatal Depression Score, the depression tool used in the SHINE trial and its follow-up
GEE	Generalised estimating equations: the technique used to explore associations that also accounts for clustering.
HAZ	Height-for-age Z-score
HCC	Health Centre Committee
HFIAS	Household food insecurity assessment scale
HDDS	Household dietary diversity score
Hb	Haemoglobin, measured in grams / decilitre (g/dl)
HIC	High income country as defined by the World Bank
HWISE	Household water insecurity experiences scale
IYCF	Infant and Young Child Feeding intervention: For SHINE this was a lipid based nutrient supplement for the child from age 6-18 months, together with monthly visits with nutrition advice.
Imp I	Impedance Index, measured by bioimpedance as a measure of relative lean mass, with units m^2 $Ohms^{-1}$
IQA	Individual Question Analysis (used for adaptation of the KABC-II)
IQR	Inter-quartile range: the range between the top and bottom quartile
KABC-II	The Kaufman Assessment Battery for Children 2nd edition.
LMI	Lean mass index, measured by bioimpedance as a measure of relative lean mass divided by $height^2$, with units $Ohms^{-1}$
LMIC	Low and Middle-Income Country
MICS	UNICEF Multi-indicator cluster survey (discipline subscale used)
MLWH	Mothers living with HIV
MOHCC	The Zimbabwean Ministry of Health and Child Care, who works in partnership with Zvitambo

MRCZ	The Medical Research Council of Zimbabwe
MPI	Mental Processing index: the cognitive total for the Kaufman Assesment Battery for children, which was the primary outcome for this follow-up study.
MUAC	Mid-upper arm circumference, measured in cm.
NCD	Non-communicable diseases (eg diabetes, hypertension)
PCA	Principal Components Analysis
Plus-EF	The Plus EF tablet-based executive function test combined 3 subtests which were: the multi-source interference subtest, stars and flowers subtest and flanker subtest.
SAHARAN	The School-Age Health, Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox includes all the school-age outcomes measured
SAP	The pre-specified statistical analysis plan, available on Open Science Framework at https://osf.io/8e2zh
SAT	School Achievement Test: the total includes the sum of the 3subtests that measure numeracy, reading and writing.
SD	Standard deviation: a measure of the spread of the data
SDQ	Strengths and Difficulties Questionnaire: A 25-item caregiver reported questionnaire which details the child's socioemotional function. 20 of the questions form the problem-based total SDQ total reported in the paper. Each subscale is detailed in supporting information
SFU	SHINE Follow-up: the abbreviation for the SHINE children who were followed up at 7 years.
SHINE	Sanitation Hygiene Infant Nutrition Efficacy cluster randomised trial
SOC	Standard of Care arm in the SHINE Trial. All trial arms including SOC had breastfeeding support to 6 months and additional support for PMTCT screening.
SOP	Standardised Operating Procedure for performing a measurement or task.
SQ-LNS	Small quantity lipid based nutrient supplementation are designed to complement the diets of children aged 6 months and older by including multiple micronutrients within a food base that also provides energy, protein and essential fatty acids.
WASH	Water, Sanitation and Hygiene intervention: For SHINE this included a latrine, field washing stations, Chlorine water treatment and monthly visits with hygiene advice.
WASH + IYCF	The combined WASH and IYCF intervention within the SHINE trial
WAZ	Weight-for-age Z-score
WG	Washington Group UNICEF tool for screening for child disability
Zvitambo	The Zvitambo Institute for Maternal and Child Health Research previously coordinated the SHINE trial and now works on a variety of projects in partnership with the MOHCC.

List of published papers

The following is a list of publications that relate to the work presented, particularly for chapter 3:

Characterising school-age health and function in rural Zimbabwe using the SAHARAN toolbox Piper J. D. Clever Mazhanga, Gloria Mapako, Idah Mapurisa, Tsitsi Mashedze, Eunice Munyama, et al. *PLoS One 2023, Vol 18, (5), p* e0285570, DOI: 10.1371/journal.pone.0285570
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0285570

The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial: Protocol for School-Age Follow-up Piper J. D, Mazhanga C, Mapako G, Mapurisa I, Mashedze T, Munyama E et al. Wellcome Open Access 2023, **8**:306, DOI 10.12688/wellcomeopenres.19463.1
https://wellcomeopenresearch.org/articles/8-306

Adaptation of the Kaufman Assessment Battery for Children—2nd edition (KABC-II) to assess school-age neurodevelopment in rural Zimbabwe Piper J. D, Mazhanga C, Mapako G, Mapurisa I, Mashedze T, Munyama E et al. *Wellcome Open Research, 2022, Vol 7 (274), DOI* 10.12688/wellcomeopenres.17902.1.
https://wellcomeopenresearch.org/articles/7-274

Impact of COVID-19 on schooling in rural Zimbabwe Piper J. D, Mazhanga C, Chidhanguro, Prendergast A. J. , SHINE Trial team. *Child: Care, Health and Development, 2022, Vol 48 (6), p.1134-35*
https://onlinelibrary.wiley.com/doi/full/10.1111/cch.12955

The current landscape and future of tablet-based cognitive assessments for children in low-resourced settings McHenry, MS, Mukherjee D, Bhavnani, S, Kirolos, A Piper JD, Crospo-Llado, MM, Gladstone MJ *PLOS Digital Health, 2023, Vol2(2) e0000196*
https://journals.plos.org/digitalhealth/article?id=10.1371/journal.pdig.0000196

1 Chapter 1: Introduction

1.1 Stunting and its consequences

Up to 250 million children are at risk of not reaching their developmental potential due to stunting and extreme poverty[1]. Stunting, which reflects poor linear growth, currently affects 22% (148 million) children under 5 years globally[2,3]. "Stunted" children are statistically defined when their height-for-age Z-score (HAZ) is more than 2 standard deviations below the global reference standard. However, linear growth faltering affects many children who have not yet fallen below this arbitrary cut-off[4]. Stunting is associated with increased mortality, reduced neurodevelopment, poorer school performance, long-term chronic disease, and lower adult earnings[5]. It is therefore considered one of the best surrogate markers of child health inequalities, and tackling stunting remains a global health priority[6]. However, the causes of stunting, its long-term consequences and design of effective interventions to reduce the global burden of stunting remain poorly understood.

Short stature is not in itself a problem, but it reflects a 'stunting syndrome' in which multiple pathological changes are embodied by reduced linear growth[6]. Stunting in children is classically viewed as the outcome of chronic malnutrition causing a poor quality of growth. However, recent analyses have shown there is substantial overlap with acute malnutrition: wasted children are at much higher risk of stunting[7], and children with concurrent stunting and wasting have a higher risk of mortality[8]. Stunting is also associated with overweight and long-term risks for later obesity, with changes towards a high-energy diet creating a 'double burden' of malnutrition, particularly in low- and middle-income countries (LMIC) such as Zimbabwe[9]. Stunting's effects are seen with acutely increased mortality, morbidity and vulnerability in childhood[10], although the underlying pathology that drives this is poorly understood. Longer-term vulnerabilities are also seen across the life course in both reduced growth, and crucially reduced function across cognition, physical function and long-term health[6,11] (Figure 1.1). This continues to be observed including in more recent longitudinal cohorts such as the 'Young Lives' cohort which has observed child growth from 2002-2016 in Ethiopia, India, Peru, and Vietnam[10].

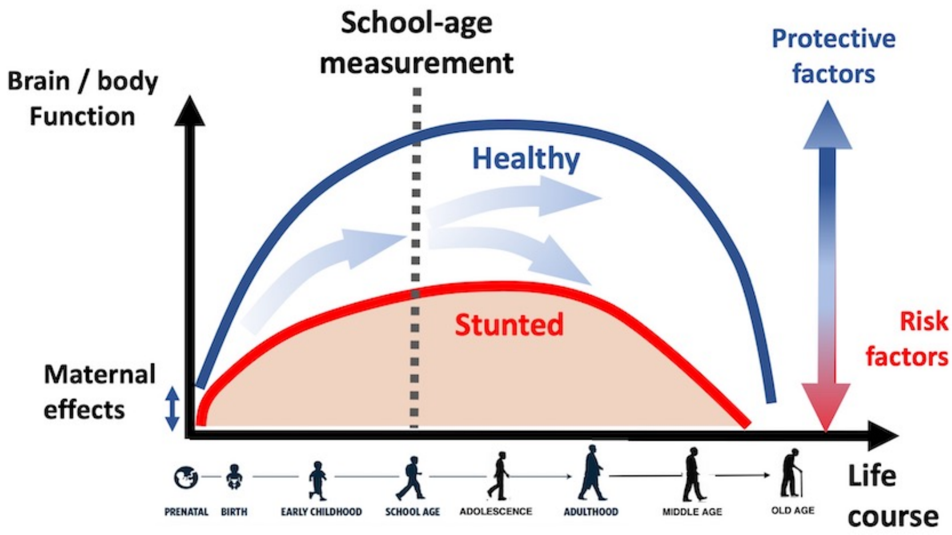


Figure 1-1 Early-life trajectories and the life course

Early-life growth and health sets trajectories across the life course. Stunting has early-life (including maternal and antenatal) beginnings and its profound effects are observed across the life course in growth and function. A healthy trajectory is shown in blue and contrasts with a stunted reduced trajectory in red, with the difference in slope noted particularly in early-life. The child's trajectories of growth and function are also affected by ongoing risk and protective factors. Early-life interventions may help to increase the protective factors (or mitigate risk factors) that improve health, physical and cognitive function. School-age measurement provides the opportunity to observe the progress so far and is also highly predictive of later adult function. From[12] and adapted from[13,14].

Children appear to be particularly sensitive to poor growth within the first 1000 days (from conception to two years of age). This time window is seen as the period when the body is both most sensitive to challenging conditions and potentially also most receptive to interventions[11]. Therefore early-life can also be viewed as a crucial time window for installing later physiological function and capacity with lifelong health effects.

The developmental origins of health and disease

The 'Developmental Origins of Health and Disease' (DOHaD) hypothesis, suggests that exposure to environmental influences during critically vulnerable periods of development has consequences on both short-term and life-long health[15,16]. The concept (previously termed 'fetal origins of adult disease') describes how the developing foetus responds if exposed to a challenging environment in-utero[16]. These challenges may be a combination of poor nutrition, inflammation, placental insufficiency or other stressors such as toxins. The foetus responds by developing adaptations for immediate survival and also programming for future survival if a similar environment is encountered in later life[16]. The most obvious manifestation is low birthweight[16], but there are also subtle, irreversible changes in development and function of multiple tissues and vital organs such as thymus, skeletal muscle, lungs, pancreas and kidney, due to disruption in gene expression and resultant growth[15]. Shorter telomere length and methylation[17] may be mechanisms for foetal programming in the uterus, including determining infant autonomic nervous system reactivity[18]. The effects of this programming are still unclear, but dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis with high levels of glucocorticoids[19] and reduced organ size[20] have been detected[15]. These adaptations also cause increased vulnerability to non-communicable diseases (NCD) in later life[21], particularly when combined with subsequent exposure to poor environmental conditions[22]. For example, higher cardiovascular mortality is observed for those from lower socioeconomic backgrounds, which is further compounded amongst those born with low birthweight[22].

High rates of NCDs are particularly noted in LMICs, which are not fully explained by the rise in traditional risk factors such as tobacco smoking, alcohol consumption, poor diet or physical inactivity[15]. These traditional and other risk factors for NCD's may be defined as a 'physiological load' that applies chronic stress and inflammation to the body increasing the risk of chronic disease. It is postulated that this physiological load may combine with early-life adversity that has pre-programmed the body to be particularly vulnerable: Hence a combined approach is to also consider prenatal and early life as forming the foundations of 'physiological capacity', which then propagates NCD risk when combined with stresses caused by a physiological 'load' [23] (Figure 1.2).

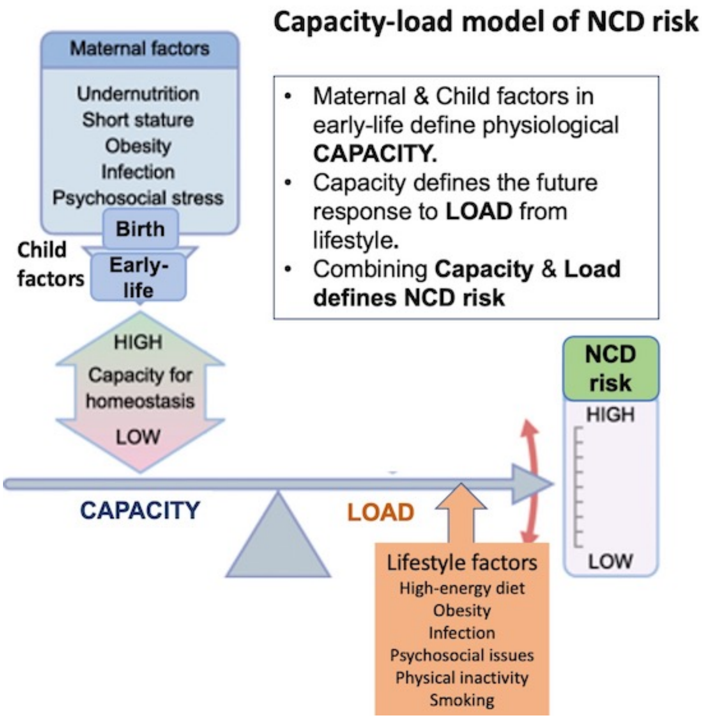


Figure 1-2 The physiological capacity-load model.

Low physiological capacity due to in-utero and early-life insults combined with a physiological load may lead to a combined mechanisms for increased non-communicable disease (NCD) risk. Adapted from[23].

1.1.1.1 Postnatal growth and body composition

Beyond low birthweight, direct markers of reduced early-life growth include lower height, and impaired physical and cognitive function. Stunting incidence has been recently shown to peak at 0-3 months, with sustained recovery from stunting rare after this age [24]. Previous studies have individually shown that poor linear growth is associated with aspects of physical function such as grip strength[25], reduced cognitive development[26] and increased cardio-metabolic risk factors[27]. Stunting in infancy is associated with long-term effects on health such as an unfavourable lipid profile at age 3-4 years[28] although there is no obvious effect on total energy expenditure[27]. Furthermore, children who are born small and then subsequently have catch-up growth can exhibit a dramatic transition towards central obesity and insulin resistance[29], potentially signifying an early programming effect which continues to prioritise fat mass.

Fat mass provides short-term benefits for survival[30], but has longer-term metabolic health costs associated with inflammation[31]. In particular, the distribution of body fat is important, with central abdominal fat associated more with chronic inflammation and NCD risk[32], whilst peripheral fat is not[33]. In contrast, lean mass associates with improved organ size[34], neurodevelopment[35] and reduced metabolic risk[36]. Skeletal muscle and lean mass are strongly associated with height[37]. Across multiple studies, stunting is associated with a reduction in lean mass, partly mediated through height[38]. The measurement of body composition which incorporates both fat and lean mass may therefore provide valuable insight into trade-offs within stunted children that may also highlight future risks to health, physical and cognitive function (Figure 1.3).

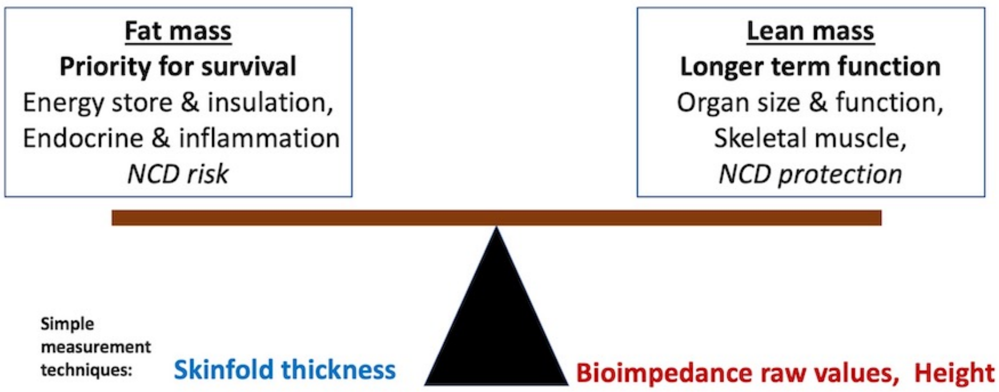


Figure 1-3 Body composition: lean and fat mass

Body composition reflects a balance between both lean and fat mass. Fat mass is required for survival to store energy and insulation, as well as having endocrine and inflammatory signals.

Lean mass is related more to height, organ size, function and muscle size, and is more protective against non-communicable diseases (NCD's). Simple measurement techniques used later are also shown with skinfold thickness for measuring fat mass and bioimpedance and height for lean mass.

Early-life height-for-age Z-score (HAZ) and stunting are often used as crude indicators of future health and development, but in general there is poor understanding of how early growth and more detailed body composition influence long-term outcomes of children.

Insights into the pathogenesis of stunting

The underlying pathology of stunting is complex, multi-factorial and poorly understood, which is reflected by the disappointing progress demonstrated with current interventions in many global regions. No intervention study has been able to normalise linear growth among children in developing countries[6]. Maternal undernutrition, poor antenatal growth, suboptimal breastfeeding and poor complementary feeding combined with micronutrient deficiencies all provide an important proximal contribution to stunting[39]. Beyond these direct nutrition-specific factors, recurrent clinical and subclinical infections lead to both acute and chronic inflammation that also re-partitions nutrients away from growth and causes malabsorption[40,41]. Maternal HIV may affect both antenatal and postnatal growth, either directly through infection or through exposure which increases the risk of stunting[42]. More distal factors include deprivation driven by sociocultural, economic and political contexts that drive inadequate household, community and societal support. Societal factors that contribute include access to healthcare and education, political stability and accountability, urbanisation and sanitation, population density and social support networks. These distal factors all impact the household's food security, feeding practices and local environment to affect children's growth and development as demonstrated in the UNICEF conceptual framework of undernutrition (Figure 1.4) [43]

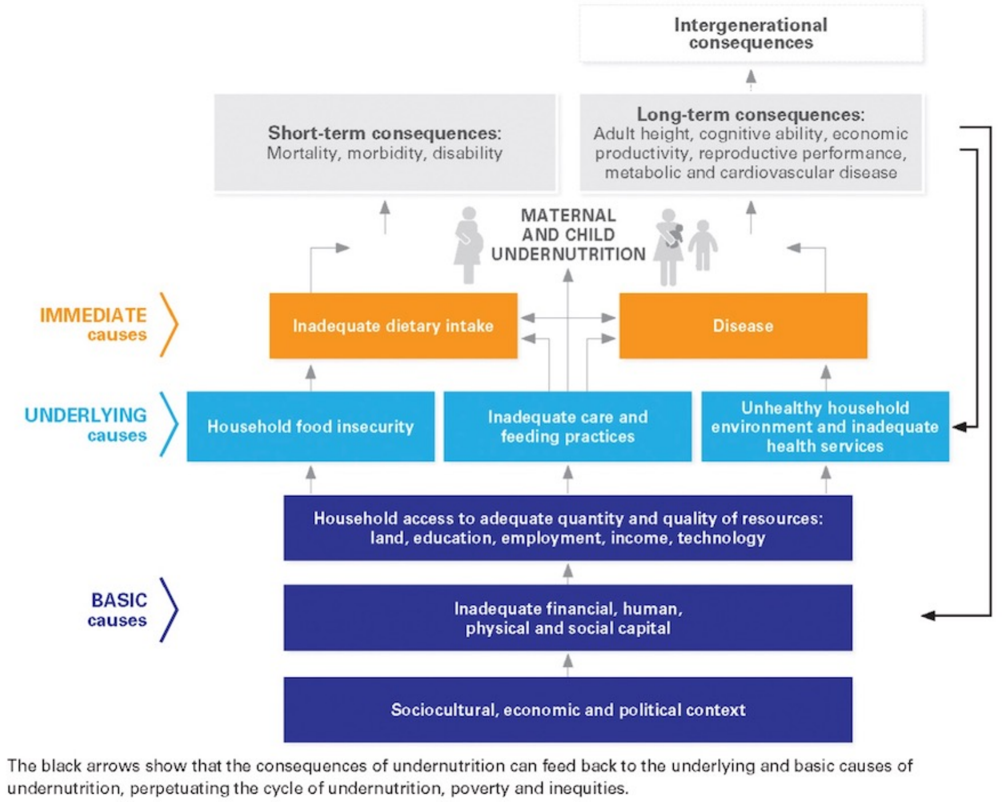


Figure 1-4 the UNICEF framework on undernutrition[43].

Immediate causes of undernutrition are inadequate dietary intake and disease, but direct underlying causes include food insecurity, inadequate care and environmental factors. Basic causes include the households access to resources, capital and the wider contextual factors.

Poor linear growth in LMIC's across the life course starts epigenetically with the mother's height being strongly associated with birthweight[44]. In optimum conditions, antenatal growth is similar across contexts: the INTERGROWTH Project showed across eight countries that foetal growth was similar amongst affluent, healthy, educated women[45]. However, LMICs have increased rates of preterm and small for gestational-age (SGA) babies, which in turn drive markedly increased risks of stunting[6]. It has been estimated that at least 20% of stunting has *in-utero* origins[46]. Maternal undernutrition and poor antenatal care contribute to adverse pregnancy outcomes[47], child mortality and stunting[48].

Healthy infants have the fastest growth velocity between birth and 6 months, when exclusive breastfeeding is recommended for its effects on mortality, morbidity and long-term cognition [49]. This period, particularly in the first 3 months after birth, also has the highest incidence of stunting[24]. However, trials that have attempted to improve stunting in the first 6 months by improving breastfeeding, such as in the PROMISE trial in Sub-Saharan Africa[50] or Suchana trial in Bangladesh[51], have had disappointing effects. This may be due to a combination of factors: Firstly, the programming effect of in-utero conditions may have already set poor early trajectories of growth. Secondly, there may be multiple simultaneous drivers of poor growth such as psychosocial adversity, poor maternal nutrition as well as inflammation in the infant[6]. This time window is currently the focus of active research to improve detection of growth faltering and care for infants under 6 months[52]. Also, there are attempts to provide breastfeeding support and supply interventions that target maternal wellbeing through enhancing relaxation, such as recently demonstrated in Malaysia[53].

The period from 6-24 months has previously been described as the most critical period of growth because of observations of worldwide timing of growth faltering in this time window[54]. Most stunting interventions focus on improving infant and young child feeding (IYCF) practices for complementary feeding (whilst supporting continued breastfeeding in this window). However, benefits are small at around 0.1 Z-score calculated from a meta-analysis of multiple trials[55]. Hence the next section examines potential interventions across different domains to mitigate poor growth.

Interventions that target stunting

Preventing stunting is a cornerstone of the global goal to end world hunger (SDG 2.2) and that all children should survive and thrive[56]. Stunting remains particularly focused in Asia (52%) and Africa (43%), with progress lagging most in Africa[3]. Hence interventions typically are implemented in these geographic areas.

Nutrition

Antenatal nutrition targeted towards mothers may improve undernutrition in pregnancy[57], but have had mixed results on children's postnatal growth, with some positive results such as the MINIMAT trial in Bangladesh[58] or when combined with infant supplementation in the iLiNS-DYAD trial in Ghana[59]. However, other results have not shown a sustained effect[49].

Most modern complementary feeding interventions between 6-24 months of age use small-quantity lipid-based nutrient supplements (SQ-LNS), which provide multiple micronutrients combined with a food base that also provides calories, protein, and essential fatty acids[60]. Small-quantity lipid based nutrient supplements (SQ-LNS) are seen as the most effective IYCF tool suitable for programmatic roll-out, with broad benefits on child growth[61], survival[62], anaemia[63] and child development [64]. They are relatively easy to store and administer to children, and hence can be used in preventing malnutrition in vulnerable populations[60]. Although, SQ-LNS have benefits across a range of contexts, recent meta-analyses demonstrate they have only modest effects on stunting[62] with gains of approximately 0.11 LAZ[62]. However, there remain very few studies that have undertaken *long-term* neurodevelopmental follow-up after SQ-LNS complementary feeding interventions. It is possible that these early-life gains in linear growth from improved nutrition may translate into significantly larger benefits in cognition, learning and physical function by school-age or later in life.

Water, Sanitation and Hygiene (WASH) interventions

Nutrition-sensitive interventions that reduce infection and inflammation, such as improvements in water, sanitation and hygiene (WASH), are another plausible approach to reduce stunting. This was illustrated previously in the UNICEF Framework for Undernutrition (Figure 1.4). It is hypothesized that WASH would decrease both symptomatic infections such as pneumonia and diarrhoea, as well as low-grade intestinal inflammation – a subclinical disorder called environmental enteric dysfunction (EED) [65]. EED is caused by dysbiosis in the gut microbiome, which also causes inflammation, morphological changes in the small intestine, loss of barrier function, and bacterial translocation from the gut[66]. Observational research exploiting cross-sectional variations in WASH has shown strong associations between diarrhoea prevalence and stunting[67-69]. The Malnutrition and Enteric Disease Study (MAL-ED) has demonstrated links between infections during childhood and physical growth and development[41]. This study also showed that subclinical infection with multiple enteropathogens, particularly *Shigella*, enteroaggregative *E. coli*, *Campylobacter*, and *Giardia*, had a substantial negative association with linear growth in the first 2 years after birth[41].

Children with access to improved sanitation may have lower rates of stunting, as observed in the Young Lives cohort[70]. However, trials that have randomised WASH interventions have had generally disappointing results: three recent randomized controlled trials showed no effect of improved WASH on growth in the first two years[71-73]. WASH strategies often have issues with poor compliance and short durations of exposure[67], although more recent trials have tried to achieve higher intervention fidelity [73]. A previous Cochrane review of WASH interventions for child growth showed a minimal impact[74]. Despite the lack of direct experimental evidence of WASH impacting growth, it is widely accepted in countries that have achieved impressive reductions in stunting (such as Brazil) that improvements in WASH have played a prominent role[75].

Child development may be more receptive to WASH interventions than is growth[76]. Measurements at 2 years of age following a WASH intervention showed no effects on cognition in Zimbabwe[77] but did in Bangladesh[78], although the Bangladesh control group had fewer fieldworker visits than the WASH group, which may have led to differences in stimulation arising from study visits. Intriguingly, one long-term follow-up study after a randomized early-life handwashing intervention which reduced infant diarrhoea in Pakistan, did show significant benefits for later neurodevelopment[79]. Another study which reduced open defecation within India’s total sanitation campaign also suggested a cognitive benefit[80]. However, an ongoing systematic review has found minimal evidence overall that randomised WASH interventions directly improve child development[81].

Poverty and adversity

Beyond low income, poverty may be viewed as a multidimensional construct of co-occurring risk factors which interact in complex ways to negatively shape child development[82]. Examples of poverty-related risks include heightened risks of food and water insecurity and infectious diseases, poor shelter and environmental contamination. Across several nations including China[83] and Brazil[75], economic growth has been associated with reduced stunting, but this depends on overall equity, with more benefits observed in the richest compared to the poorest wealth quintiles[84]. Increasing consumption of high-energy foods following economic growth, especially in the context of previous poor growth, can also lead to rising obesity[83]. Economic growth may also enable child height to improve beyond that expected with short mothers. For example, in the COHORTS study of 7630 mother-child pairs from Brazil, Guatemala, Philippines, India and South Africa, economic growth was attributed to explain the observation that children had on average taller heights than their mothers[44].

It is increasingly recognised that adverse child experiences (ACE), such as abuse, caregiver mental illness, and household adversities have both immediate and long-term consequences for child development and health, with poverty being a concomitant risk factor[85]. Harmful psychological stressors include chaotic living arrangements, stressful events, and exposure to household or community violence[82]. Recent evidence is emerging for effective interventions for these adversities: for example, a recent cluster-randomised trial among poor families in Rwanda demonstrated improved caregiver-child interaction, reduced harsh discipline, improved hygiene behaviours, and reductions in caregiver depression and anxiety following a home-visiting intervention. This programme taught elements of nurturing care, paternal engagement, stress management, conflict resolution, and nonviolent discipline to male and female caregivers[86]. These all helped to provide an environment more conducive to child development[86].

Multiple future threats are posed by climate change and environmental degradation which may impact nutrition, WASH and poverty as well as ACE[85]. ACE are very common, and may affect up to half of the global population, with cascading effects on child growth, development and ongoing well-being[87]. This may also include less severe and commonly experienced stressful life events, which nevertheless may carry signs of biological damage such as accelerated aging as measured by methylation[88]. UNICEF estimates that 1 in 4 children under the age of 5 years are in a household with intimate partner violence, whilst 3 in 4 children aged 2-4 years may experience physical punishment by their caregivers on a regular basis[89]. Interventions to prevent and mitigate these risk factors include sectoral reforms to provide support across society[83], as well as encouraging nurturing care to support mothers to stimulate their children. Nurturing care interventions have previously been shown to improve child development but have a negligible impact on child growth in a recent meta-analysis[76].

1.2 Importance of long-term follow-up

There is little understanding of the longer-term impact of early-life interventions aimed at improving growth and development. This is due to a paucity of studies that have undertaken longer-term cohort follow-up, and an absence of holistic assessments combining neurodevelopment, physical function and growth at older child ages. Height at 2 years is the point that has been identified worldwide as indicating established faltering growth[54]. This can be a strong predictor of later human capital[90]. Although there is little evidence that WASH reduces stunting in early life, growth is not a reliable proxy for neurodevelopment and it is plausible that WASH may have a longer-term impact on functional outcomes, even in the absence of growth effects. However, assessing the sustained efficacy of early-life interventions requires long-term follow-up to measure later functional outcomes. This may provide additional insight beyond a short-term measure of growth. A comprehensive assessment is vital to understand growth and function trajectories across different domains, as well as the impact of risk and protective factors. This can help characterise the overall sustained impact of interventions.

It remains unclear whether small gains in height or function in early life following interventions may lead to improved function and metabolic health at school-age. Small effects on growth of protein supplementation aged 0-24 months in the INCAP trial in Guatemala translated into highly significant differences in school achievement and later adult earnings when measured in later life[91]. Although there was no impact on height, a second long-term follow-up of a psychosocial stimulation intervention on stunted children in Jamaica also showed a benefit of increased earnings[92]. Both of these long-term follow-up studies have subsequently informed policy on the economic benefits of early-life intervention[93], in part because of a continuing lack of alternative long-term follow-up studies.

Importance of holistic school-age follow-up

The lack of data evaluating *combined* neurodevelopmental, physical fitness and growth outcomes has led to a call for further studies that can measure a range of outcomes[60,76]. A combined battery of tests that measures body composition, growth and physical function has previously been demonstrated to be feasible and informative in the ChroSAM study for chronic survivors of malnutrition[94]. Understanding school-age trajectories with a holistic assessment that incorporates different functional domains can inform potential interventions, especially in the context of risk and protective factors. School-age allows more detailed assessments of cognitive development, including executive function and socio-emotional behaviour[95]. For example, a nutrition trial that gave LNS between 6-18 months showed a benefit in socio-emotional development at 4-6 years in Ghana[95]. School performance including literacy and numeracy is itself a valuable functional outcome that can only be evaluated at school-age. Therefore school-age assessments are more predictive of adult cognitive function, particularly as more advanced domains such as executive function can be better assessed[96].

School-age is an optimum time for holistic indicators, because cognitive functional outcomes emerge that are more predictive of adult outcomes[5,97], whilst physical function[98] and body composition[99] may help to predict NCD risk[23]. At school-age there still remains considerable potential for interventions to improve catch-up growth and function[100,101] beyond the most vulnerable first 1000 days[6]. Beyond 2 years of age, there is also increasing evidence of benefit in linear growth for micronutrient and protein interventions, particularly in children with previous linear growth faltering[102]. Follow-up ideally should include birth cohorts so that previous early-life growth and environmental exposures are well-understood. In addition, birth cohorts do not select children based on school attendance, which may disadvantage those from marginalised groups, including disabled children. Contemporary conditions should also be measured alongside school-age growth and function: recent studies have suggested that childhood trends in height and BMI growth are highly variable in response to different social, nutrition and environmental factors[103].

School-age measurements and their risk and protective factors would increase understanding of the long-term effectiveness and timing of interventions to address growth, physical, cognitive, and socioemotional development in LMICs[104]. Improved IYCF is currently seen as the most effective intervention for stunting during the vulnerable window between 6-18 months of age[105], but as mentioned before, only increases linear growth modestly (average +0.11 HAZ)[55]. A recent systematic review showed early-life nutrition interventions have benefits for neurodevelopment, but growth itself is not a reliable proxy for functional outcomes[76]**.** The review emphasised the need for long-term follow-up that measure both growth and development of optimised complementary feeding[106], and WASH intervention studies

Assessing the impact of catch-up growth

The potential benefits of catch-up growth are also poorly understood. Some recent research has shown that post-infancy growth recovery can be associated with improved later child cognition and is associated with maternal height and socio-economic status[107], but other studies find no effect[108] or mixed effects with increased NCD risk markers such as blood pressure[109]. Early-life HAZ is currently used as a crude indicator of future health and potential across the life-course. However, linear growth failure and how its potential recovery influence the long-term outcomes of individual children is not understood. The extent of catch-up growth in height and head circumference is variable across studies, with lasting deficits also remaining[110,111]. Moreover, the effect of stunting or catch-up growth within a broader understanding of body composition has also not been characterised.

The period from 6-24 months is classically seen as one of the most critical intervention windows for child growth[54], in part because it represents the peak decline in HAZ due to inadequate complementary feeding. Timing of growth failure closely correlates with later body composition and function. Birth weight has consistently been associated with subsequent lean mass[36,112], whilst infant body composition predicts later body composition, obesity and other cardiometabolic outcomes[113]. Timing of catch-up in weight therefore appears to be important: beyond early childhood, additional weight gain has been associated with increased fat mass and subsequent adult obesity[36]. Recent evidence suggests that targeted early-life nutrition interventions increase lean mass[114]. Lean mass accretion in infancy may also have other functional benefits, including neurodevelopment[35]. However, faster weight (and not height) gain after two years may be associated with fat mass[109]. Therefore, there remains the possibility that some early-life nutrition interventions may also promote catch-up growth that is less advantageous: LNS may potentially increase fat mass in stunted children and therefore increase NCD risk in the longer-term, since faster weight gain after two years is associated with increased risk of chronic disease[109]. The quality of growth depends in part on prioritisation of different areas of the body through mechanisms that are poorly understood[115]. Although lean mass benefit has been demonstrated in cohort studies[35,38], body composition techniques can explore if a randomized complementary feeding intervention not only increases height, but also positively increases lean mass, physical and cognitive development.

HIV exposure

Progress towards ending vertical HIV transmission in sub-Saharan Africa has led to increasing coverage of prevention of mother-to-child transmission (PMTCT) interventions. However, given the high incidence of maternal HIV, the population of children who are born HIV-free (CBHF) is increasing: these children are HIV-negative, although born to HIV-positive mothers. Global estimates of CBHF have risen from 14.8 million in 2018[116,117], to 15.9 million in 2021[118]. Before antiretroviral therapy (ART), worse clinical outcomes were noted for CBHF than children who were HIV-unexposed (CHU) (ie born to HIV-negative mothers). These included up to 3-fold higher mortality, together with higher severity and occurrence of common infections[119,]. There was also an impact on growth, with more linear growth failure and higher rates of stunting in CBHF compared to CHU[119,120]. In the PMTCT era with maternal and neonatal use of ART, clinical outcomes of CBHF have been more uncertain due to few long-term studies. However, data emerging from sub-Saharan Africa confirms that these differences in growth and health persist in early life despite high coverage of PMTCT interventions.

CBHF continue to have poorer neonatal outcomes, with increasing likelihood of premature birth, and small-for-gestational age[121]. These disparities continue so that by 2 years of life, CBHF have poorer neurodevelopment[122] and a higher frequency of stunting[123]. There are likely multiple factors that contribute to these clinical disparities, including both universal risk factors (eg psychosocial adversities) and HIV-specific risk factors (eg exposure to co-infections and inflammation) [124] and mechanisms through which they operate may be shared (Figure 1-5).

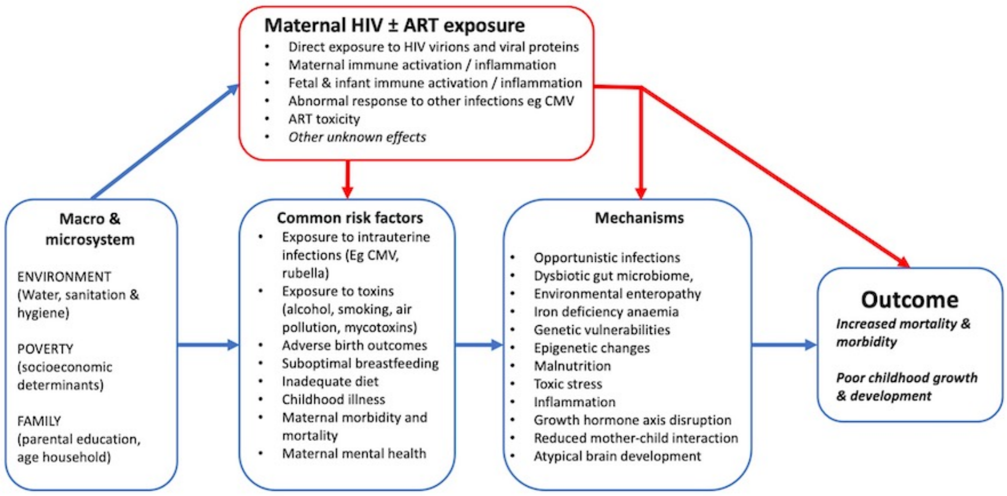


Figure 1-5 Conceptual framework of exposures for CBHF

Conceptual framework suggesting potential mechanisms through which maternal HIV exposure may affect children born HIV-free (CBHF). CBHF's mortality, morbidity, growth and development may be affected by multiple pathways. Red lines show HIV-specific pathways whilst blue lines represent universal pathways that may propagate disadvantage. Adapted from [42]

Therefore CBHF are likely to have both prenatal and early-life exposures including maternal HIV, ART, opportunistic co-infections, inflammation, dysbiosis, malnutrition and psychosocial stress that may propagate persistent effects long after the antenatal exposure has ended. Evidence of this is accumulating with recent MRI scans showing differences in brain structure shortly after birth[125].

In a recent meta-analysis of nearly 5000 children under 5 years from 8 high-quality studies, CBHF continued to have small impairments in expressive language development and early-life gross motor function[126]. However, there are currently very few studies that have conducted long-term follow-up of CBHF to determine whether the observed early-life disadvantages persist to school age. One study of cognitive development across five African countries found similar scores between CBHF and CHU groups at median age 7 years[127]. This study used the KABC-II, measures of attention such as the Test of Variables of Attention (TOVA)[128] and BRIEF executive function questionnaire[129], but did not evaluate language and literacy, which are also key for predicting future function[127]. Another study in Zambia found reduced growth in CBHF by 7.5 years of age compared to CHU[130]. Other studies have reported decreased IQ among CBHF in south-east Asia[131] and reduced mathematic scores[132]. However, most studies have measured a limited range of outcomes without simultaneously examining growth, cognitive and physical function in CBHF.

The SHINE cluster randomised trial

The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial (clinicaltrials.gov NCT01824940) was motivated by two main hypotheses[133]. Firstly, that a major cause of child stunting and anaemia was environmental enteric dysfunction (EED) which provided chronic inflammation from increased gut permeability. Secondly, that the primary cause of EED was infant ingestion of faecal microbes due to living in conditions of poor quality and quantity of water, sanitation and hygiene (WASH)[133]. Hence it was hypothesised that combining improved WASH with improved infant and young child feeding (IYCF) may provide significant additional benefits for child growth and anaemia, more than individual WASH or IYCF interventions. Therefore the primary objective of SHINE was to determine the independent and combined effects of improved household WASH and improved IYCF on length and haemoglobin concentration among children at 18 months of age[133].

SHINE was designed as a 2x2 factorial cluster randomised trial across 2 contiguous districts (Shurugwi and Chirumanzu) in rural Zimbabwe. Households were usually single-family dwellings surround by farmland, with a mean distance between households of 82.6 m, and an average of 18.6 people per square km[73]. Clusters were designed based on the catchment area of 1 to 4 community health workers (CHWs) and the trial deployed a constrained randomisation technique to achieve balance across the groups for 14 variables related to geography, demography, water access and community-level sanitation coverage[73,133,134]. Women were eligible if they became pregnant during the recruitment period and lived permanently in one of the study districts.

SHINE study interventions

Women recruited into SHINE had 15 CHW visits from enrolment to 12 months post-partum (averaging 1 visit/month). The nutrition and hygiene intervention modules were developed based on detailed formative work[135-138]. From 13 to 17 months, CHW's performed visits every month as part of their routine care and also to deliver intervention supplies (eg SQ-LNS, water chlorination and soap). The CHW's also delivered informal reminders about relevant behaviours in WASH and nutrition. CHW supervisors checked implementation fidelity with both spot-checks and timed visits.

Ethical approval was provided by the Medical Research Council of Zimbabwe (MRCZ/A/1675) and Johns Hopkins University Bloomberg School of Public Health. Clusters were randomised to 4 different arms:

1) **Standard of care (SoC):** A strengthened community health workers (CHW's) system encouraged exclusive and prolonged breastfeeding promotion for all infants from birth to 6 months[137], combined with consolidated PMTCT services. This strengthened CHW system also improved antenatal care, family planning and immunisations.
2) **WASH:** Standard-of-care intervention *plus* a Blair ventilated improved pit latrine, which was built within 6 weeks of enrolment and two 'tippy-tap' handwashing stations, that were installed by 32 weeks' gestation. There were also regular deliveries of water chlorination solution (WaterGuard, Nelspot, Zimbabwe) and liquid soap until the SHINE infant was 18 months old. To protect the infant born in the SHINE study from geophagia, a plastic baby mat and playpen were also given. The CHW also delivered WASH intervention modules encouraged handwashing with soap, safe faeces disposal, avoidance of geophagia in infants, chlorination of drinking water, and hygienic complementary food preparation.
3) **IYCF:** Standard of care interventions *plus* 20 g/d of SQ-LNS (Nutriset, Malaumay, France) for children from age 6–18 months, and monthly nutrition modules delivered by CHWs promoting

optimal use of locally available foods for complementary feeding, with nutrient-dense, diverse infant diets after 6 months, continued breastfeeding, and feeding during illness.

4) **IYCF & WASH:** Standard of care interventions *plus* all IYCF interventions *plus* all WASH interventions.

Figure 1-6 The SHINE trial

The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Cluster randomised trial a) Map of Zimbabwe showing the approximate location of the study districts Shurugwi and Chirumanzu b) The 2x2 factorial design showing. IYCF: Infant and Young Child Feeding, WASH: Water, Sanitation and Hygiene, SoC: Standard of Care c) Map showing the clusters within the districts. Note that white areas were not suitable due to either a very low population density or peri-urban settlement.

SHINE study measurements

Mothers were enrolled in early pregnancy, with detailed data collection on home, maternal, birth and early-life factors. At the baseline visit, which occurred from 2012 to 2015, pregnant mothers had their height, weight, haemoglobin and mid-upper arm circumference (MUAC) measured, as well as multiple environmental covariates. HIV testing was offered and performed using a rapid test algorithm at baseline, with additional testing offered at 32 gestational weeks and 18 months postpartum. All women testing positive for HIV were referred for antiretroviral therapy. The early-life child HIV status was measured by dried blood-spot DNA polymerase chain reaction (PCR), plasma RNA PCR, or rapid test algorithm, depending on child age and sample type. It was pre-specified that all outcomes were stratified by maternal HIV status. The baseline questionnaire also measured household minimum dietary diversity, food insecurity (Coping Strategies Index), household wealth using a locally validated composite wealth index[139], and maternal capabilities including depression, gender norms and social support[140].

Research nurses then visited at 32 weeks' gestation, and 1, 3, 6, 12 and 18-months post-partum to measure child growth and assess maternal and household characteristics. Health records were used to record birth details including birth date, weight and delivery. SHINE study nurses measured infant weight and length at 1 month, then head circumference and MUAC were additionally measured at 3 months, and all these measures were subsequently measured with postnatal visits up to 18 months of age. All visits also evaluated intervention compliance: WASH-related behaviours were recorded by maternal report as well as observation of the handwashing station, latrine and play space (i.e. if they were present and with signs of appropriate use such as a trodden path to the latrine). IYCF behaviours were assessed through 24-hour recall of infant diet which included the SQ-LNS as well as maternal report of continued feeding during illness. For equity at the 18-month endpoint, households in the non-WASH arms had a latrine constructed.

SHINE Study early-life results

Overall, 5280 pregnant women were enrolled from 211 clusters across both districts between 2012-2015, and 3686 children born to HIV-negative mothers (CHU) were assessed at 18 months. Key findings for the children randomised in the SHINE study were that the IYCF intervention increased mean length-for-age Z-score (LAZ) by 0.16 (95% CI 0.08, 0.23), and reduced stunting prevalence by 21% (from 35% to 27%), while the WASH intervention had no effect on linear growth[73]. IYCF also increased haemoglobin concentrations by 2.03 g/L (95% CI 1.28, 2.79), but WASH had no effect[73]. These findings were consistent with two other concurrent trials that were designed in partnership with SHINE to provide household WASH and IYCF (The WASH Benefits trials) in Bangladesh[71] and Kenya[72]. SHINE and WASH Benefits data have contributed to recent meta-analyses of the effects of SQ-LNS on child growth[61] and anaemia[63] which confirm the positive impact of SQ-LNS across multiple contexts.

Child development at 2 years of age was also measured in a sub-study of 1655 HIV-unexposed children, using the Malawi Developmental Assessment Tool (MDAT) to measure gross motor, fine motor, language and social skills; the MacArthur Bates Communicative Development Inventories (CDI) to assess vocabulary and grammar; and the A-not-B test to test object permanence. The interventions showed minimal impact of IYCF or WASH on all neurodevelopmental measures at age 2 years[77].

Within Shurugwi and Chirumanzu districts, the prevalence of maternal HIV was approximately 15%. For 668 children born HIV-free (CBHF) to HIV-positive mothers, the IYCF intervention increased mean LAZ by 0.26 (95% CI 0.09, 0.43) and haemoglobin concentration by 2.9 g/L (95% CI 0.9, 4.9)[141]. Intriguingly, for 318 CBHF in the 2-year child development substudy, CBHF in the combined IYCF and WASH arm had higher total MDAT scores (mean difference +4.6; 95% CI 1.9 to 7.2) and MacArthur Bates vocabulary scores (+8.5 words; 95% CI 3.7 to 13.3), compared to the standard of care arm, but there was no evidence of effects from IYCF or WASH alone[142]. Overall, the SHINE trial had shown initial benefits in early-life growth and anaemia for IYCF which were greater in CBHF than CHU. However, it was unclear if these benefits would be sustained as children became older.

1.3 Long-term follow-up of the SHINE Trial

Children born in the SHINE trial provide a unique opportunity to understand how the first thousand days may influence both early-life growth and development and later school-age functional outcomes. This is within a population with a high prevalence of stunting and childhood adversities, a significant sub-population born to HIV-positive mothers, and results from an IYCF intervention that had modest beneficial effects in early life. Although the WASH intervention had no demonstrable effects in early-life, the opportunity for long-term follow-up also remains important[76].

To date, there have been minimal long-term follow-up studies after early-life stunting interventions, particularly in Sub-Saharan Africa. The key study of long-term follow-up for nutrition interventions on stunting was the INCAP study in Guatemala, from 50 years ago. The results from INCAP suggested that early-life improvements in nutrition and growth provided long-term benefits in cognition[91]. At a village-level of randomisation, children in INCAP who received additional nutrition in the form of a protein drink by age 2 years initially had only modest benefit in neurodevelopmental scores. This benefit was amplified in long-term follow-up, demonstrating that those who received the nutrition intervention had higher IQ scores, greater work capacity and earnings (among men) and greater schooling (among women)[5]. The findings from the INCAP study remain important but further research is required in more contemporary settings: INCAP was conducted in the 1970s, when global stunting prevalence was much higher: 50% of the Guatemalan study population had severe stunting (HAZ < - 3). This may have reflected inter-generational stresses and may not be representative of current worldwide stunting. By contrast, contemporary rates of stunting show 22% children have moderate stunting (HAZ < -2)[3]. Due to the high rates of severe stunting in the 1970's, there was a much greater impact of the INCAP intervention on linear growth than that commonly seen in intervention trials in the past 20 years of complementary feeding interventions (+0.62 HAZ compared to +0.11 HAZ[55]). The INCAP trial provided an important proof-of-concept that complementary feeding interventions that achieve a large benefit in growth can additionally have important long-term physical and neurodevelopmental benefits. However, the situation currently in the world is that stunting prevalence is mainly concentrated in Africa and Asia. Moreover, severe stunting is now relatively rare, but moderate stunting remains widespread with a prevalence of 20-40%. As a result of high rates of moderate stunting, the average impact of interventions is also less, with typical benefits of complementary feeding interventions on HAZ of only 0.1 to 0.2[55].

Overall, long-term follow-up studies that reflect contemporary levels of stunting as well as its geography and modern interventions such as SQ-LNS are urgently needed. More contemporary follow-up can then inform cost-effectiveness analyses and if benefits are shown, provide important advocacy for both complementary feeding and nutrition-sensitive interventions such as WASH policies and programming.

There have been several other examples of benefit demonstrated in long-term follow-up which were not observed in the short term. For example, long-chain polyunsaturated fatty acid supplementation among children in the USA showed no effect on cognition at 18 months but a significant impact at 6 years[143]. Beyond nutritional supplementation, follow-up of Mexican children 8-10 years after a trial of conditional cash transfers showed an improvement in socio-emotional development[144]. Long-term effects have also been observed following antenatal interventions such as micronutrient supplementation in rural China[145] and antibiotics in Malawi[146].

Most research studies and programme evaluations have relied on shorter-term proxy outcomes such as stunting prevalence or linear growth by age two years[147]. Hence, it is also plausible that the lack of suitable holistic, long-term measurements may have underestimated the impact of nutrition, WASH and / or agricultural interventions to date.

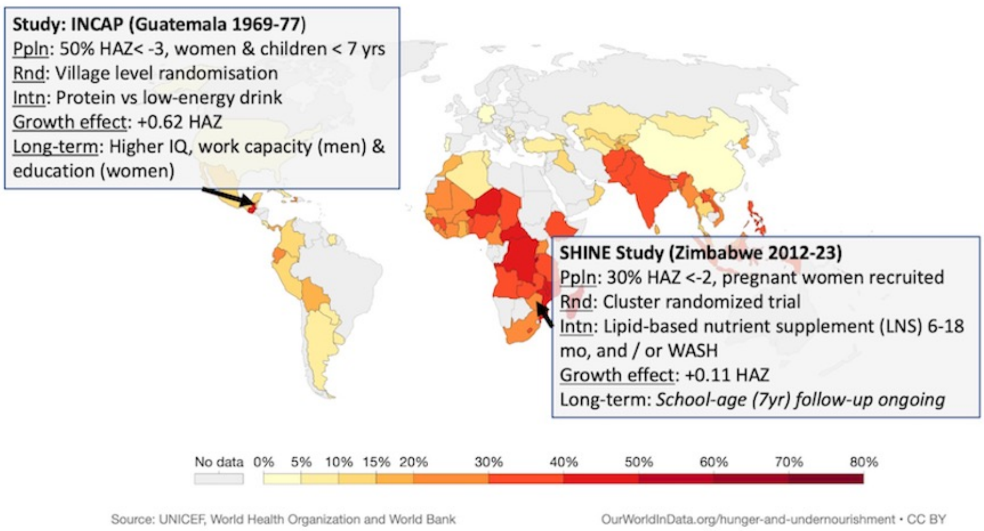


Figure 1-7 The importance of long-term follow-up

The importance of long-term follow-up of intervention trials on stunting reflecting contemporary conditions. The INCAP study used a protein drink to achieve impressive growth and long-term effects but used a village-level randomisation and reflected conditions in the 1970s. The SHINE study reflects more contemporary conditions, interventions and growth effects in Sub-Saharan Africa, from[12].

The SHINE cohort represented the optimum conditions for intervention against stunting in several ways. First, a meta-analysis of nutrition interventions showed postnatal multiple micronutrients and macronutrients (similar to that implemented in SHINE) resulted in the biggest effect size in early child development when compared with prenatal or single micronutrients[148], and a Cochrane review and meta-analysis suggested that SQ-LNS (as given in SHINE) were the most effective complementary feeding intervention for stunting[60]. Second, SHINE interventions achieved one of the highest reported exclusive breastfeeding rates between birth and 6 months, thereby laying the foundations for optimum child development[137]. Third, SHINE was one of the few trials globally to randomize an integrated household WASH intervention based on combining water treatment, hygiene education, latrine construction and reducing faecal exposure among children. Finally, the SHINE cohort collected detailed meta-data from the first 1000 days including antenatal exposures, birth outcomes, maternal demographics, socioeconomic status, caregiver capabilities, early-life longitudinal growth, and intervention fidelity. This enabled adjusted analyses to comprehensively evaluate the effects of early-life growth, WASH and IYCF interventions and the impact of maternal HIV exposure at school-age.

It was also plausible that the interventions may demonstrate reduced effect with longer follow-up so that there was no significant difference in function or metabolic health between nutrition and control arms. This would still provide important evidence to extend early-life interventions beyond focusing purely on early complementary feeding and household WASH. Either way, the importance of long-term follow-up of clinical trials that give an accurate measure of overall effect is increasingly recognised[149,150].

In summary, long-term follow-up studies reflecting contemporary conditions, geography and interventions for stunting remain urgently needed to inform IYCF and WASH policies and programming in LMICs, including among the vulnerable population of children born HIV-free. Taken together, there is a recognised need to understand how early-life public health interventions influence school-age functional outcomes, including predictors for later adult cognitive function, health and risk of future chronic disease[36,151]. School-age follow-up of the SHINE trial provides a unique opportunity to characterise the long-term impact of early-life conditions including IYCF and WASH interventions.

2 Chapter 2: Aims & hypotheses

This thesis describes the measurement and analyses of growth, cognitive and physical function among children who were born into the SHINE trial and were 7 years old during the follow-up study between April 2021 to October 2022. Chapter 2 outlines the key aims and hypotheses for these analyses. Chapter 3 describes the techniques used to measure school-age growth and function in rural Zimbabwe, including a pilot study in 80 children who were not in the SHINE trial, to create an integrated battery of tests, called the SAHARAN toolbox. Chapter 4 explores the dataset among children born to mothers living without HIV (i.e. Children HIV-unexposed or 'CHU') and includes associations with contemporary exposures of growth and environmental conditions. Chapter 5 explores associations with early-life exposures of growth (including catch-up growth) and environmental conditions for CHU. Chapter 6 describes comparisons in growth, cognitive and physical function between children born HIV-free (CBHF) to mothers living with HIV and those born to mothers living without HIV (CHU). Chapter 7 explores associations of the SHINE early-life IYCF and WASH interventions with child outcomes for CHU. Chapter 8 includes an overall discussion of the results, their implications, and future directions for research and policy.

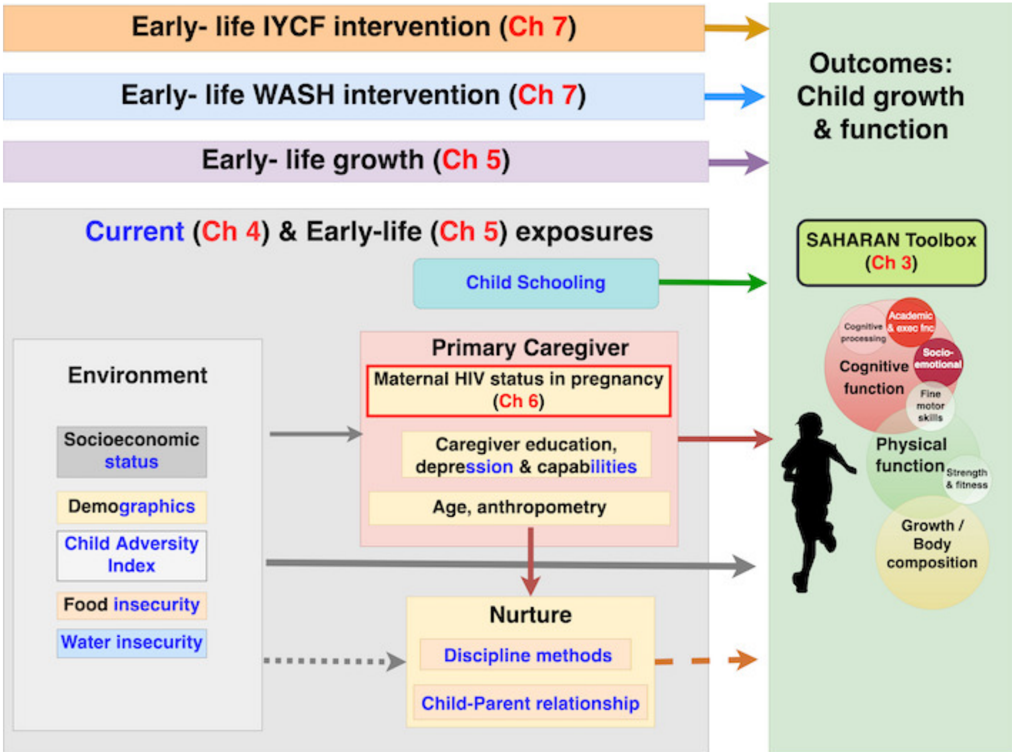


Figure 2-1 Conceptual framework of SHINE Follow-up

Conceptual framework describing contemporary and early-life exposures on child growth, cognitive and physical outcomes for the SHINE cohort as assessed by the SAHARAN toolbox. Exposures were categorised into nurturing, maternal, schooling and environmental domains. Early-life exposures are labelled in black and contemporary exposures in blue text, with measurements of both early-life and contemporary showing text in both colours. Outcomes were based on the SAHARAN toolbox to describe school-age growth, cognitive and physical function for children at 7 years old. Links for the conceptual framework to each chapter are described in red text. SAHARAN, School-age Health, Activity, Resilience, Anthropometry and Neurocognitive; IYCF, infant and young child feeding; WASH, water, sanitation and hygiene. Adapted from [12]

Therefore this thesis has the following aims and hypotheses tested in the subsequent chapters:

Aim 1 (Chapter 4): Explore contemporary determinants of school-age growth, cognitive and physical function

Hypothesis: Contemporary growth and environmental factors have strong associations with school-age growth, cognitive and physical function.

Aim 2 (Chapter 5): Explore early-life determinants of school-age growth, cognitive and physical function

Hypothesis 1: Early-life growth faltering is negatively associated with subsequent growth, cognitive and physical function at age 7 years.

Hypothesis 2: Catch-up growth enables a gain in physical but not cognitive function

Hypothesis 3: Early-life household, maternal and nurturing exposures are associated with school-age growth, cognitive and physical function.

Aim 3 (Chapter 6): Explore the impact of HIV exposure on school-age growth, cognitive and physical function

Hypothesis: Children born HIV-free have poorer growth, cognitive and physical function compared to children who are HIV-unexposed.

Aim 4: (Chapter 7): Determine the impact of early-life nutrition and WASH interventions on school-age growth, cognitive and physical function

Hypothesis: An infant and young child feeding intervention delivered between 6-18 months of age increases growth, cognitive and physical function of children at age 7 years, whilst WASH has no effect.

3 Chapter 3 Methods: Characterising School-age growth and function

3.1 Introduction

One reason for limited school-age data on growth, health, physical abilities, and cognitive function is a shortage of feasible and reliable tools. This chapter initially describes the constructs of interest within measurements of school-age cognitive function, growth and physical function. It then introduces the conceptual framework where the interplay of these measurement domains is postulated, which forms the basis of this thesis. Secondly, the COSMIN framework is described to inform the selection of the cognitive primary outcome, the Kaufman Assessment Battery for Children (KABC-II). Thirdly, the selected tools are combined to create the School-Aged Health Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox and its training and community sensitisation described. Fourthly, the detailed methods and initial results exploring validity from a pilot of the SAHARAN in 80 children are presented. Fifthly, the adaptation of the main cognitive tool, the KABC-II within the pilot study is also described. The sixth section details main SHINE follow-up trial procedures and methods applicable to the subsequent results-based chapters.

3.2 Constructs of interest

School-aged Cognitive function

Combining several tools that measure individual cognitive domains is the most effective way of assessing cognitive function[12]. Children in low and middle income countries (LMIC) may have multiple negative exposures (eg undernutrition, socioeconomic adversity and lack of psychosocial support[152]). These may be mitigated by protective factors such as nurturing, nutrition and stimulation[153]. These multiple factors may also have differential combined and individual impacts on the various domains within cognition.

3.2.1.1 *Child functional summary*

A questionnaire may provide a useful indication of overall child function. This can determine difficulties in mobility, sight and hearing, as well as behaviour and learning[154]. By highlighting any difficulties, it provides an overview that is complementary to specific areas of cognitive function. However, careful training on judgement of disability and its impact may also be required.

3.2.1.2 *Cognitive processing*

Traditional assessments such as intelligence quotient (IQ) testing often rely on measuring *acquired knowledge*. These Westernised tools were validated in settings with high enrolment and attendance rates at school: their application to LMIC settings may be problematic, particularly in areas with variable schooling enrolment and attendance[155]. Instead, tools that measure *learning potential* may be preferred in these environments, which measure underlying learning and problem-solving skills necessary to solve novel tasks. This may also be less sensitive to cultural and schooling bias[155,156]. This is defined as 'cognitive processing' and requires tests that measure across several domains including spatial reasoning, problem solving, short and long-term memory.

3.2.1.3 *Academic skills*

Traditional measures of educational achievement still remain important predictors for later academic and socioemotional function[157]. Including them therefore gives measures of cognitive function that are complementary to cognitive processing. These include:

i) Literacy: Assessment of language is highly indicative of neurodevelopment including literacy, behaviour and socioemotional function[158]. Reading at an early age enables children to absorb more advanced skills and content. Otherwise, children typically have reduced educational achievement[159]. Similarly, writing proficiency including the child's own name[160] or individual words have also been associated with emergent literacy skills[160] and early-grade schooling exposure[161].

ii) Mathematical skills: Mathematical literacy (including numeracy) is a core life skill[162]. Hence school-age mathematical capabilities are similarly associated with later engagement, learning and educational achievement[163].

3.2.1.4 Executive function

Executive function measures advanced cognitive function including working memory, attention, inhibitory control and cognitive flexibility[164]. It is highly associated with school readiness in young children,[165] later educational outcomes[166], socioemotional function[165] and academic skills[157,165]. With appropriate design, these functions may be viewed as culturally universal skills[96] and therefore a tool that can specifically measure executive function was included.

3.2.1.5 Behaviour and Socioemotional function

Externalising behavioural problems such as attention deficit hyperactivity disorder have been rarely measured in LMIC[167], but occur in up to 9% of preschool children in high-income settings[168]. Child mental health, which may include behavioural measures is also increasingly recognised as an important function and predictor of later adult mental health[169]. Socioemotional, academic, executive and cognitive function are clearly inter-related both in early childhood[170] and adolescence[171]. Therefore, a measure of socioemotional function was also included. In school-age children, this is often indirectly measured through interview of caregivers or teachers[167,172].

3.2.1.6 Fine motor function

Fine motor function is an important cognitive skill, and stunted children have previously been shown to have slower hand coordination[173]. Reduced fine motor coordination has also been associated with low birthweight and reduced socioemotional function[174], as well as reduced academic ability[175]. These combined effects may contribute to delayed neurodevelopment[176].

Overall, it was important to include multiple different measures of cognitive function that covered numerous domains.

School-aged physical function

Child physical function and health are best assessed by combining separate measures of cardiovascular fitness, muscular strength and body composition[12], as demonstrated in recent systematic reviews[177,178]. For example, cross-sectional data have shown that both muscle strength and cardiorespiratory fitness in children are associated with reduced risk factors in later life for cardiovascular disease (including lower blood lipids, adiposity and blood pressure)[177,179]. Body composition is also affected: increases in muscular strength from childhood to adolescence are inversely associated with overall adiposity[177]. Therefore, physical function measurements should include measures of muscular strength as well as cardiovascular fitness.

The ALPHA[178] and PREFIT[180] test batteries formed the basis for the physical function tests selected. The choice of tests was based on a recent systematic review[181] combined with knowledge from a previously successful pilot in Malawi (Marko Kerac, personal communication). Physical fitness may be a powerful marker both of contemporary child health and future cardiovascular risk[179]. In high-income settings, there is also some emerging evidence of physical activity being associated with improved cognitive ability[182]. The rising trend of obesity and overweight in sub-Saharan Africa in combination with undernutrition (the ‘double burden of malnutrition') means there is increasing interest in studies that combine measurements of strength, physical fitness[183] and body composition.

Growth

Evidence is emerging that stunted growth in early life affects later height, body composition and physical parameters such as blood pressure[184,185]. Measures of body composition at school-age and adolescence (for example body mass index, waist circumference and skinfold thicknesses) are associated with later cardiovascular risk factors such as high blood lipid levels and carotid artery narrowing[177]. Healthier body composition in childhood and adolescence lowers the risk of death in later life[177]. Interventions that solely improve linear growth, are only weakly associated with cognitive function, according to a recent systematic review and meta-analysis[76]. Lean mass at birth may be associated with improved socioemotional function, and fat mass may decrease it according to one study[186]. This probably reflects maternal life history trade-offs that are then reflected in her offspring[187]. Overall, it was clear that both anthropometry and body composition should be measured to gain further insights into the quality of growth and its impact on child function[12].

Initial Conceptual framework

A conceptual framework was developed based on the relationships discussed previously between a child's environment, growth, physical and cognitive function (Figure 3.1).

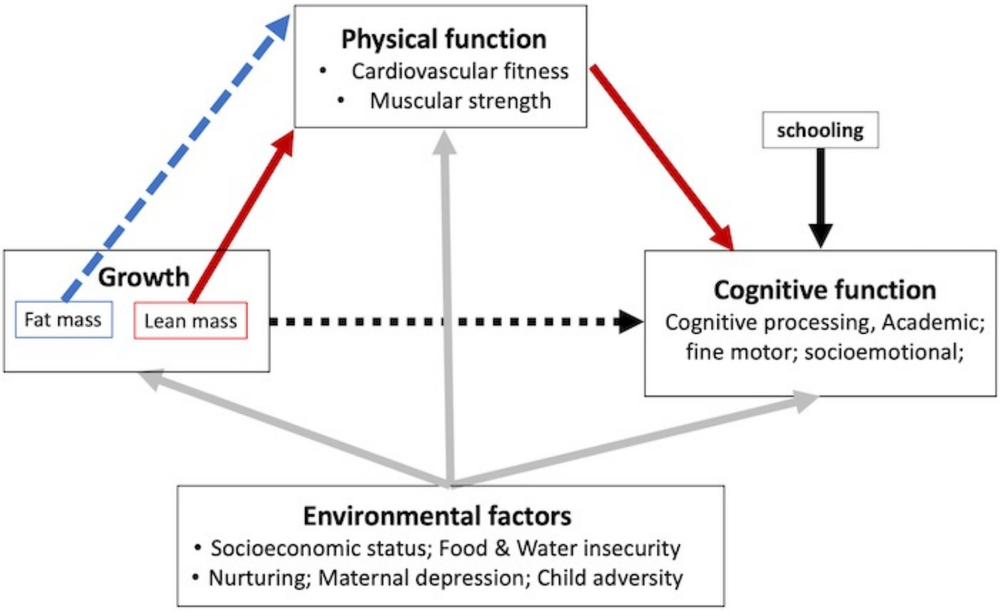


Figure 3-1 Conceptual framework for school-age

Conceptual framework describing child growth, cognitive and physical function domains. Environmental factors likely impact all 3 domains. Adapted from[12]

The School-Age Health, Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox was designed to characterise school-age health and function[12]. In addition, a detailed caregiver questionnaire enabled adjusted contemporary covariates in this conceptual framework to be explored (Chapter 4) and adjusted models applied (Chapters 4 and 6). After this characterisation of school-age growth and function, associations could be explored with the contribution of early-life factors (Chapter 5, 6 and 7), antenatal exposure to HIV (Chapter 6) and the SHINE study early-life interventions (Chapter 7).

3.3 Choice of tools for the SAHARAN toolbox

Overall process

A stepwise approach was performed for selecting the tools for the SAHARAN toolbox that would measure cognitive function, physical function and body composition:

1. A detailed literature review identified systematic reviews describing tools for measuring cognitive function[76,188,189], a recent toolkit published by the World Bank[14], and a test battery for physical function[178,181].
2. Individual assessment tools were screened for their use in LMICs[95,190] using selection criteria based on the COSMIN tool[191] (Fig 3-2, Appendix 3-1 & 3-2).
3. A range of international child development, nutrition and sports science experts were contacted to provide their opinion on each domain and tool. The experts provided further information on the content validity and applicability of the shortlisted tools for a rural sub-Saharan African context (Appendix 3-2)[94].
4. After this initial selection, pre-testing, cognitive interviewing and piloting of instruments was performed. This led to further adaptation and a narrowed selection of tests for the final toolbox (Fig 3-3).
5. A detailed pilot of 80 children was then conducted. Within the pilot, construct validity and internal consistency were assessed by examining the relationships between different tests within similar cognitive domains (convergent validity), as well as relationships between growth and physical function[192].

COSMIN assessment and choice of KABC-II

The COSMIN tool was used for assessing a tools' validity, reliability, interpretability and responsiveness (Figure 3-2).

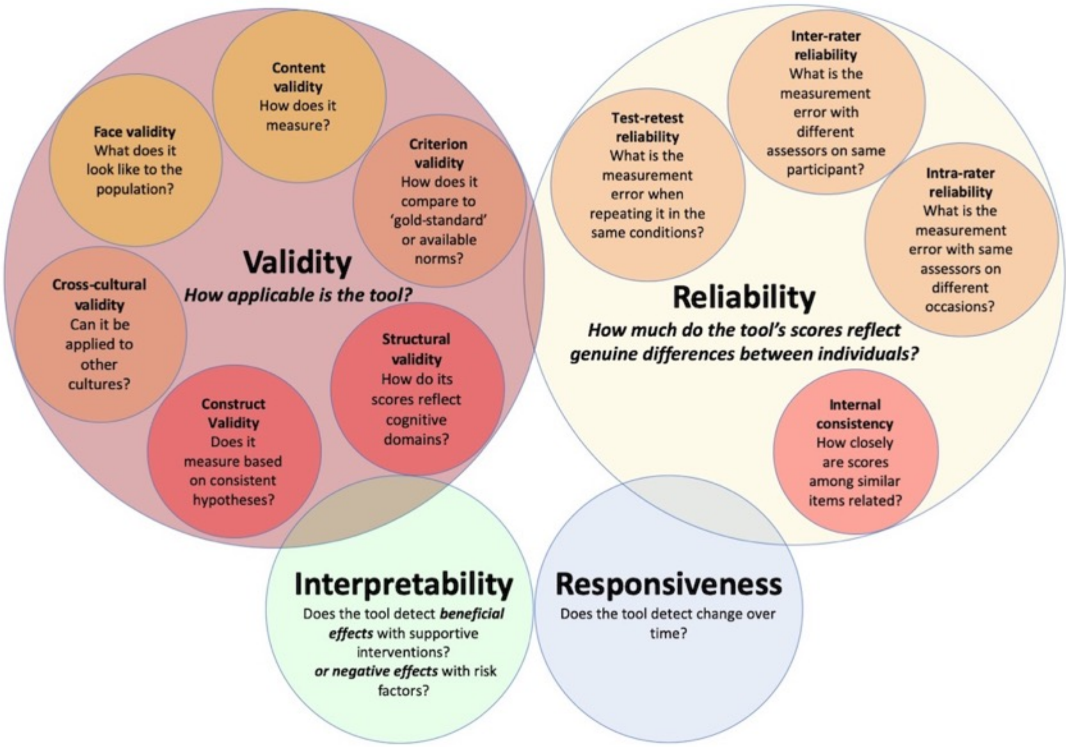


Figure 3-2 Assessing tools using the COSMIN criteria.

Diagram from[193]

An example of this process is the choice of the Kaufman Assessment Battery for Children 2nd edition (KABC-II), which was chosen as the primary outcome for assessing the impact of the SHINE IYCF intervention on cognition (Chapter 7).

The KABC-II was chosen as the primary outcome for the following reasons:

1. **Age (7 years and over):** Its broad age range of 5 to 18 years enables effective measurement of a range of cognitive domains, as well as consistent follow-up as the cohort ages.
2. **Applicability (previously used in LMIC):** It has been widely used across multiple African countries and languages[188], including using Shona in Zimbabwe[194] and rural South Africa[190] on children at a similar age. Therefore in-country field experience was available for training.

3. **Availability:** The tool is available from Pearson and training in Shona was possible in Harare. Online training via Zoom was provided from expert trainers in Uganda, Malawi and South Africa.
4. **Face validity:** Initial reactions to the KABC-II tool demonstration from Zvitambo staff as well as the Shurugwi District Health Executive (DHE) were positive. In particular KABC-II's theoretical approach is based on Luria's neuropsychological model: this uses domains of cognition which minimize the bias of school exposure[190]. Therefore, KABC-II was highly suitable for the Shurugwi context where school enrolment and attendance were highly variable, which was further exacerbated by the COVID-19 pandemic.
5. **Cross-cultural validity;** KABC-II was developed in USA, but subsequent studies have since adapted and validated it for LMIC in India[195], Uganda[196] and rural South Africa[190]. The rural South African context[190] replicated findings from the normative sample, and maintained the KABC-II factor structure during analysis. Rural South Africa closely resembles the SHINE study setting[73].
6. **Content validity:** The Luria approach is designed to simultaneously assess cognitive processing using the interaction between three key areas (attention, coding new information and planning behaviour). Together these provide problem-solving skills to the novel puzzles in the KABC-II, which rely less on acquired or taught knowledge from schooling[197].
7. **Construct validity and reliability:** The KABC-II was developed using rigorous psychometric evaluation in the USA where it demonstrated construct validity and reliability in a sample of 3025 children[198] with a Cronbach alpha of 0.9. These findings were replicated in the USA[199] and multiple other countries[190,195,200]. Reliability of the KABC-II has been further demonstrated within multiple African rural settings (including Zimbabwe) by using a video-based monitoring system (Quali-ND) of quality control[194].

8. **Interpretability:** The KABC-II has also demonstrated it can detect differences in outcome in keeping with child adversities. Children living with HIV performed significantly worse across South Africa, Zimbabwe, Malawi, Uganda in a multi-site study[127]. Similarly in separate studies in Burkina Faso, both stunted children[201] and those exposed to alcohol in pregnancy[201] performed significantly worse.
9. **Criterion validity and responsivity**: There is no gold standard measure for child development, partly because it is highly context specific, so criterion validity could not be determined. Similarly, responsivity is problematic since no studies were found that have repeated KABC-II measurements in the same sample.

The selection for other tools based on COSMIN principles is described in Appendix 3-1. A list of experts that were contacted to provide further advice is described in Appendix 3-2.

3.4 The SAHARAN toolbox

The SAHARAN toolbox comprises a single assessment conducted with the child and caregiver, focused on cognitive function, growth and physical function (Fig 3-3). A short film describing it use is at: https://www.youtube.com/watch?v=4869Zy90wyg

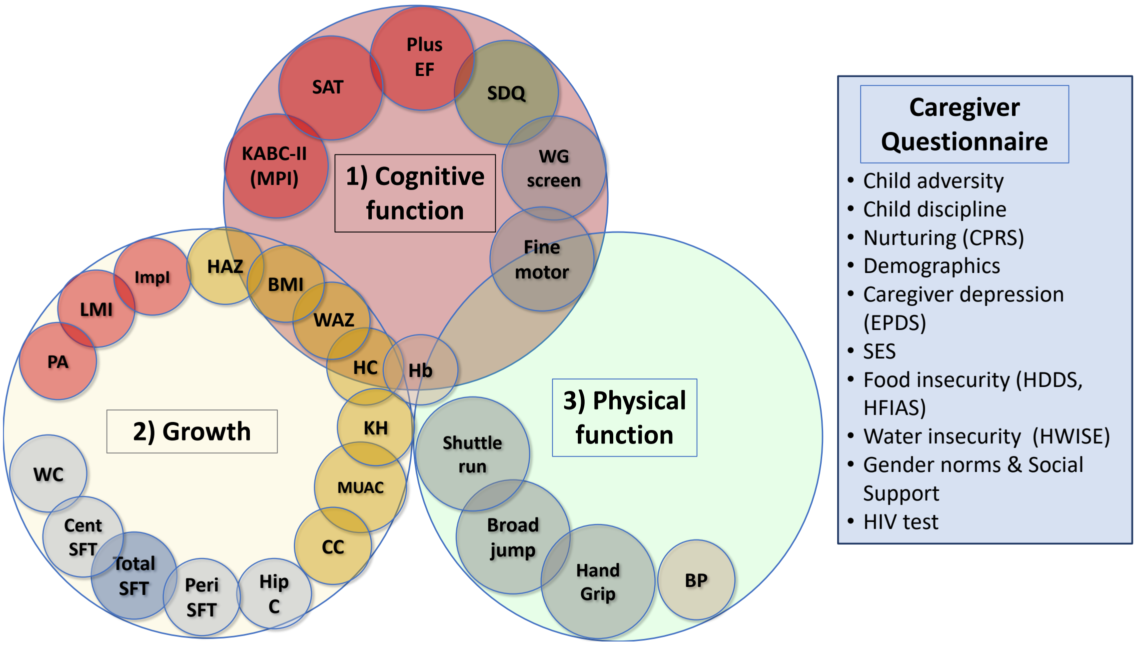


Figure 3-3 The SAHARAN Toolbox

The SAHARAN toolbox: A 4-hour holistic assessment comprising child growth, body composition, cognitive and physical function assessment with simultaneous caregiver questionnaire.

1) Cognitive function: KABC-II: Kaufmann Assessment Battery for Children 2nd edition, with the total used as the MPI: Mental processing Index. SAT: School Achievement test. Plus EF: Plus EF tablet-based executive function. SDQ: caregiver-reported Strength and Difficulties Questionnaire. WG screen: caregiver-reported disability screen. Fine motor: Finger tapping time, seconds.
2) Growth: HAZ: Height-for-age Z-score, BMI: Body mass index, WAZ Weight-for-age Z-score, HC: Head circumference, cm, KH: Knee heel length, cm, MUAC: Mid upper arm circumferenc, cm. CC: calf circumference, cm. Hip C: Hip circumference, cm. WC: waist circumference, cm. Impl: Impedance Index, m^2Ohms^{-1}. LMI: Lean mass index $Ohms^{-1}$. PA: Phase angle, ^{0}. Cent SFT: Central skinfolds: mm, Total SFT: total skinfolds, mm. Peri SFT peripheral skinfolds, mm. Note that anthropometry measures have a yellow background, lean mass have a red background (measured from bioimpedance), and fat mass have a blue background. (skinfolds and central circumferences).
3) **Physical function** Shuttle run: maximum level in 20 m shuttle run test. Broad jump: distance in standing jump, cm. Hand grip: Average grip strength, Kg force. BP: blood pressure, mm Hg. Hb: Haemoglobin g dl^{-1}
4) **The Caregiver questionnaire** Child adversity, Child discipline, CPRS (Child parent relationship scale), Demographics (household and primary caregiver information), EPDS (Edinburgh Postnatal Depression score), SES (Socioeconomic status), Food and water insecurity, Gender norms and social support, and HIV testing.

Initial Ethical approval, Data collector training and Pre-testing

Ethical approval for the pilot study was obtained from the Medical Research Council of Zimbabwe (MRCZ/1675/A). For the pilot study, four data collectors were recruited and trained along with the project lead in a co-production process where all members contributed to translations, modifications and explanations (Fig 3-4a). Pre-testing of questions and data collector training with role plays (Fig 3-4b, c, d) formed an important step in SAHARAN toolbox development (Fig 3-3). This included role plays on precautions to protect from COVID-19 (Fig 3-4b) that ensured adequate handwashing, explanation of wearing masks and scrubs, as well as checking that participants did not have any COVID symptoms.

Figure 3-4 SAHARAN toolbox development

Flowchart and diagram of SAHARAN toolbox development**.** a: Training and modifications, b: COVID-19 handwashing roleplay for the families, c: Data collectors practising cognitive measurement with KABC-II, d: Data Collectors role-play the caregiver questionnaire with Likert scales, e & f: Community Health Worker sensitisation at Zvamabande district clinic. HCC: Health centre Committees, DHE: District Health Executive

Cognitive interviewing of the caregiver questionnaire was performed in Harare and Shurugwi on 8 mothers of different ages (27 to 62 years), which led to a variety of changes in the caregiver questionnaire and consent form including:

1) Re-phrasing of questions in Shona for clarity (eg clarification of mobile phone ownership for within the whole household)
2) Development of pictorial references for Likert scales
3) Use of a stick to point to Likert scales, and pencil to point to answers of child cognitive puzzles, thus minimizing touch and reducing COVID-19 exposure.
4) Correction of body composition description to avoid use of word 'nyama' (meat) to describe lean mass, which was culturally problematic.

These changes were approved in an ethics amendment by MRCZ (MRCZ/A/1675), 31st July 2020.

Sensitisation of the community and training of CHW's

A detailed presentation and demonstration to the District Health Executive (DHE) was provided, so that all the measurements could be explained. A community sensitisation sheet was widely distributed, together with separate sensitisation sessions for the Health Centre Committees and District Chiefs. Community health workers (CHWs) were extensively trained to describe the purpose and type of measurements (Fig 3-4e), particularly using the community sensitisation sheet and live demonstrations, including on the CHWs themselves (Fig 3-4f).

COVID-19 adaptations

The following adaptations were made to protect participants and data collectors, and minimise risk of COVID-19 transmission:

1) A handwashing station was set-up at the households and all participants and data collectors repeatedly washed their hands with soap (Fig 3-4b and Fig 3-5a)
2) Facemasks were routinely worn by data collectors and given to all participants, both caregiver and child (Fig 3-5a, c).

3) Social distancing of 1 to 2 metres was observed and measurements were performed outside (Fig 3-4d, 3-5b and Fig 3-5c).
4) Data collectors wore scrubs over their uniform (Fig 3.4b) and plastic shoes. They changed from these at the end of the visit.
5) Data collectors and participants were screened for symptoms and their temperature recorded every day.
6) All equipment was disinfected at the end of the visit, using local bleach (Jik) at WHO recommended concentration, mutton cloths and mop.
7) Strict protocols regarding self-isolation and quarantine of contacts were developed at Zvitambo Institute for Maternal and Child Health.

3.5 Overall method

The SAHARAN toolbox was designed to be used in the community using portable equipment (Fig 3-5). A handwashing station was erected and facemasks distributed, in line with district COVID-19 policies. One or two tents were pitched close to the household with 4 folding chairs, where the caregiver and child could see each other at all times. The child cognition measurements were administered in the tent using a folding table. Data were collected using Open Data Kit (ODK)[202] on tablet computers (Samsung Galaxy Tab A) for most measurements, enabling appropriate data skips and plausibility checks; some cognition measurements used paper forms (KABC-II, School Achievement Test) and the Plus-EF cognition tool recorded data directly onto the tablet computer.

Figure 3-5 Application of the SAHARAN toolbox.

a: Portable handwashing station and role play for child and caregiver, b: Tent arrangement for caregiver and child (here using a tree for shade), c: Child cognitive measurement using the School Achievement Test (SAT). d: Child body composition measurement using Bioimpedance Impedance Analysis (BIA). Figure adapted from supported information from[192].

Screening, consent and assent

All assessments were conducted by data collectors (DCs), who were primary care nurses extensively trained in study activities. On the day of the assessment, the CHW introduced a pair of DCs to the household. Screening was undertaken to ensure the child was a suitable age of 7 years for the pilot and had not previously been in the SHINE trial. Detailed consent and assent were obtained by performing a tour of all the equipment to be used combined with demonstrations prior to completing the consent and assent forms. The tests below were described in the order they were administered to the child.

Cognitive function

The following tests for cognitive function were used:

	MARKER	MEASURE	OUTCOMES	RATIONALE
Cognitive Function (120 mins including KABC-II)	**Kaufman Assessment Battery for Children 2nd edition (KABC-II)**	**Cognitive processing**	**Primary outcome: Mental processing index (MPI)**	**Overall measure of cognitive function**
			Secondary outcomes: KABC-II domain scores, individual subtest scores	Short & long-term memory, planning, problem-solving, sequential memory
	School Achievement Test	Academic	Total score, Subtest scores (*numeracy, reading, writing)*	Literacy & numeracy
	Fine motor	Shortest time to complete finger tapping sequence	Time for dominant hand, non-dominant hand, and average between both hands,	Fine motor
	Plus-EF Tablet test	Executive Function	Overall score, individual subtest scores, reaction time	Executive function
	Child socio-emotional questionnaire	Home support	Total score, sub-score removing food insecurity question	Child's own perspective on home support
	Washington Group Child function module (asked in caregiver questionnaire)	Disability screening, including vision and hearing	Overall score, disability, learning, mental health subscale	Child functional abilities
	Strength and Difficulties Questionnaire (SDQ, asked in caregiver questionnaire)	Socioemotional function	SDQ total score and subtest scores	Behaviour

Table 3-1 Tests of cognitive function, from[12]

1a. The sum of 8 core subtests within the *Kaufman Assessment Battery for Children 2nd Edition (KABC-II)* was the primary outcome for cognition, called the mental processing index (MPI)[190]. This was adjusted for age in 4-month blocks, with younger children scoring slightly higher scaled scores for the same raw score. The KABC-II is available from www.pearson.com. In order of measurement, the subtests selected were Atlantis, Story completion, Number recall, Atlantis delayed, Rover, Triangles, Word Order and Pattern Reasoning[190].

Permission was given to translate the KABC-II from Pearson, and further adaptations were made in the field for 2 subtests (Story completion and pattern reasoning, see Section 3.7). Two additional subtests (hand movements and block counting) were initially included and then subsequently dropped during the pilot study, both to reduce the assessment time and also because the MPI could be calculated without them[190]. Online training was provided by data collectors and trainers on Zoom based in Uganda, Zimbabwe[127] and South

Africa[190]. Data collectors first practised on each other in English and then Shona (Fig 3-4c). Following this, pre-testing and practice sessions were performed with children from neighbouring households. The KABC-II was adapted for use in rural settings using a Shona and Ndebele translation that was printed, laminated and spiral-bound on easels for ease of administration and cleaning between participants (Fig 3.6a, c, d).

Figure 3-6 Use of the KABC-II in a rural community setting**.**

a: measurement tent in rural household b: demonstration during maternal consent and child assent c: KABC-II equipment showing folding table, chair and KABC-II easel d: novel question from pattern reasoning "pattern plus" being administered. Adapted from extended data and results from [236]

1b. *The School Achievement Test (SAT)* was initially designed around the Early Grade Reading Assessment (EGRA)[203], but low literacy levels proved demoralising for some children. Therefore the SAT was re-designed to include some numeracy questions from the Early Grade Maths Assessments (EGMA)[163], the UNICEF MICS Foundational Learning Skills Module[204] and writing tasks of letters and words, including awarding marks for the child writing their own name[160]. The general structure was based on asking questions of increasing difficulty, in a similar manner to tests that were used in school-aged follow-up of the WASH Benefits trial[78] (Tofail F, personal communication). Further adaptations during the pilot included selecting the appropriate font and syllables that were common in teaching reading for Shona and Ndebele. During the test, the child started with numeracy, generally starting with simple questions on counting that helped to settle the child and provide confidence. The child then moved to reading letters first, then syllables and thirdly words in the child's preferred language (In the pilot 79/80 children chose Shona, one child chose English). Finally, the child was asked to write certain letters and words. Discontinuation rules were built into the test so that children who could not read basic letters did not have to read any further than single letters, similarly children who could not recognise figures did not have the mathematical questions requiring figures asked.

1c. Fine motor was assessed using sequential finger tapping from thumb to little finger. The shortest time to complete the task of tapping each individual finger once and then repeating this 6 times in a row was the primary outcome. The explanation and technique was guided by sharing training videos during pre-testing (Dr Chang-Lopez, personal communication)[205]. The data collector demonstrated first, then the child practiced several times with feedback until their technique was adequate and they could do it 3 times in a row. This ensured they could perform sequential finger tapping without stopping. After this, each child was timed to see how fast they did sequential finger tapping 6 times in a row. They repeated this for a total of 3 times on each hand and the fastest time was used. The average between the 2 fastest times for each hand was also calculated and this was used for later analysis.

1d. The Plus-EF tablet-based executive function tool is an open-source android-based cognitive assessment that uses the touch screen to measure both accuracy and reaction time. It was developed and validated for school-aged children in America[166]. It was then further adapted for use in urban and rural Kenya[206] and this was the Plus-EF version used in this study. It measures executive function including cognitive flexibility and inhibition using 4 different tasks, of which 3 were used in this study (Multi-Source interference test (MSIT), stars and flowers, and flanker subtests). Their combined accuracy score was the outcome used for this subtest. The digit scan backwards test was too advanced for children as it required a high level of numeracy, hence this was not included. The Plus-EF is designed so that before each task, the child does training subtests with the data collector. This enabled the child to become used to the touchscreen, even if they had not used one before. The DC supported by demonstrating how to hold the tablet in a standardised way (one hand each side of the tablet with thumbs free) and providing further standardised explanations. The training subtests on the tablet also provided instant feedback, to ensure standardised training and understanding before each timed assessment. The total Plus-EF score was derived by summing the accuracy scores from the tests taken together (excluding the practice tests).

1e. *The Child Socioemotional Questionnaire* asked the child directly five questions about their socioemotional support within the home without the caregiver being able to hear, together with one question on food security. Four of the questions had been previously asked to children during an evaluation of a teacher's support program in Zambia (MPES)[207]. In addition, 2 questions were previously asked to children during a pilot study for UNICEF called Healthy Promoting Schools (HPS) (Dr Lisa Langhaug, private communication). Cognitive interviewing and pre-testing of the questions was performed before they were asked in the pilot. This ensured that the questions were appropriate and understood by the child.

1f. The Washington Group / UNICEF child functioning module (WG) was used as an international tool to help identify children with functional difficulties[208,209]. This was previously correlated with the validated Malawi Development Assessment Test (MDAT) score[210] at 24 months of age[208] in rural Zimbabwe. The version for older ages was translated and back-translated. Before piloting, cognitive interviewing and pre-testing of these questions was performed. The WG provided a caregiver-reported measure of functional difficulties in the child's vision, hearing, mobility, communication, learning and behaviour. To assist the caregiver, a laminated pictorial Likert scale was used.

This adaptation was developed during the cognitive interviewing and pilot to help visualise responses. A measure of functional difficulties and severe functional difficulties enabled potential children with caregiver-reported disabilities to be identified[208] and this was correlated with additional comments recorded by the DC at the end of the form.

1g. The Strengths and Difficulties Questionnaire (SDQ) was applied as a brief caregiver-reported questionnaire to measure child mental health and behavioural problems. The SDQ asks the caregiver to describe their child's behaviour during the past 6 months, using 25 questions and has previously been used from ages 3 to 16 years. Responses were scored on a laminated pictorial Likert scale from 0-2 to give a "Total difficulties score" which was the main outcome for this tool, with subtests as a secondary outcome. The tool is available to download free in English from https://www.sdqinfo.com/.

Body composition and anthropometry

The following tests for body composition and anthropometry were used:

	MARKER	MEASURE	OUTCOMES (secondary)	RATIONALE
Body composition (20 mins)	Bio-impedance analysis (BIA)	Impedance of tissues	Lean mass index, Phase angle, Impedance index, Reactance, Resistance	Quality of growth, metabolic health
	Knee-heel length	Tibial growth	Median Knee-heel length	Prioritization of growth
	Triceps, scapular, supra-iliac, calf skinfolds	Subcutaneous fat	Sum of skinfolds, Individual skinfolds, Peripheral: central skinfolds,	Subcutaneous fat: peripheral vs. central, metabolic health
Anthropometry (15 mins)	Height, weight	Growth	HAZ, WAZ, BMI	Growth, nutritional status, Metabolic health
	Head circumference	Brain volume	Head circumference	Prioritization of growth
	Waist and hip circumference	Abdominal size	Waist circumference, hip circumference	Nutritional status, metabolic health
	Calf circumference, Mid-upper arm circumference (MUAC)	Peripheral fat & muscle	Calf circumference, MUAC	Quality of growth

Table 3-2 Tests of body composition and anthropometry, from[12]

2a. Bioimpedance analysis (BIA) provides an impedance reading (*Z*), where $(\text{Height})^2/Z$ is defined as the 'impedance index', providing a composite marker of muscle and organ mass relative to height[211]. The absolute lean mass requires a population-specific equation using another body composition technique, typically deuterium dilution[212]. Phase angle was used as a marker both of cell mass and tissue health[73,213]. Dividing by $(Height)^2$ provides the Lean mass index (1/Z), which removes the need for the population-specific equation. Lean mass index (LMI) can be also described as the lean mass component of body mass index. The Bodystat 1500 MDD or Bodystat 500 instruments (BodyStat, Isle of Man, UK) were used to measure BIA in children lying down in a standardised and neutral position (Figure 3-5d). BIA measurements were performed with electrodes attached to the right hand and foot. Readings were checked with standard criteria to ensure repeatability: Data were excluded if the phase angle was more than 8 degrees[214], or Z had poor repeatability (> 6 Ohms difference). The mean of the two readings was used for each BIA measurement. All children tolerated the BIA assessments extremely well, although a few measurements were missing due to either equipment problems or children with severe disability being unable to lie down.

2b. *Skinfold thickness* was measured using a skinfold caliper (Holtain, Crosswell, Wales) with a precision of 0.2mm. The median of 3 readings was used. All measurements were performed on the right side. Again, these measurements were tolerated well by children in the study (Fig 3-7a). For the pilot, triceps, subscapular and calf circumferences were performed. For the main study, supra-iliac skinfold thicknesses were added.

2c. *Knee-heel (tibial) length*: a commercial knemometer (weighandmeasures.com, Olney, USA) assessed the median tibial length on the right side.

2d. *Anthropometry*: A Shorrboard (Weigh and measure, USA) was used to measure height with a precision to the nearest millimetre. To ensure a flat surface, a circular spirit level (Taskar, UK) and home-built wooden base board were used. Portable weighing scales (Seca, Germany) were used to measure weight to the nearest 50g. All circumferences were obtained using anthropometry tapes (Weigh and measure, USA), following a standardised SOP, to a precision of 1 mm.

Physical Function

The following tests for physical function were used:

	MARKER	MEASURE	OUTCOMES (secondary)	RATIONALE
Physical Function (30 mins)	Grip strength (a)	Lean muscle both hand	Highest grip strength, Standardised grip strength (a) Dominant and non-dominant hand strength,	Lean muscle: hand
	Broad jump (b)	Truncal muscles	Maximum distance, standardised distance (b)	Lean muscle: leg
	20m Beep test (c) (composite score = standardised a+b+c)	Physical Fitness,	Shuttle run test level Standardised shuttle run test level: (c) *Composite standardised score = a+b+c, (pilot only)*	Stamina, Overall composite score
	Haemoglobin	Anaemia	Hb	Physical fitness
	Blood pressure (BP)	Fitness	Resting Systolic & diastolic BP, Pulse pressure, systolic & diastolic BP & pulse pressure 1 minute after exercise; Post-exercise difference between 1st and 5th BP systolic & diastolic measurement	Cardiovascular fitness

Table 3-3 Tests of physical function from[12]

3a. *Handgrip strength:* The digital Takei dynamometer (Takei, Japan) was used due to its documented validity and reliability[215]. The handgrip size of the dynamometer was adjusted appropriately for the handspan[216]. Handgrip strength was measured for the child with the elbow extended[215]. Therefore, the child stood and held the Takei dynamometer vertically downwards and squeezed as hard as they could for up to 5 seconds (Figure 3-7b). They repeated this three times for each hand, with suitable breaks between each effort. The maximum value measured was used for analysis.

3b. *The broad jump:* The child stood with their toes just behind a line marked on the ground at 90^0 using the knemometer as a set-square to the 20-meter tape measure. With their feet slightly apart, a two-foot take-off and landing was used where the child swings the arms and bends the knees to provide forward drive. The research nurse demonstrated first, and then the child also practised to ensure a good technique. The distance jumped was defined from the starting line to the back of the heels (i.e. the nearest point of contact on landing) (Figure 3-7c). Measurement from the back of the heels to the tape was similarly performed at right angles using the knemometer as a set square. The maximum jump from 3 attempts was used for analysis.

3c. *Shuttle run test (SRT):* A 20-meter tape measure was placed in the most suitable flat part of the household's outside ground. A rechargeable Bluetooth speaker (Anker Soundcore Mini, UK) was placed at 10 meters and connected to the tablet computer. After describing the test to the child, a voiceover provided a countdown. Then the child and data collector ran repeatedly between each end, arriving before the beep, with increasingly shortened time gaps between beeps (Figure 3-7d). The data collector ran with the child for the first 3 bleeps to provide the appropriate pacing. The "Beep test" free android app (Beeptest, Ruval Enterprises, Canada) was used. The caregivers and data collectors shouted encouragement to the child to encourage maximum effort. Once the child missed the beep three times in a row or stopped running due to tiredness, the child then withdrew. The test provides a valid and reliable prediction of the VO_{2max}[217], the maximum rate at which the body uses oxygen during exercise. To obtain VO_{2max}, the Leger regression equation[218] was used. This equation had previously been used to examine the effect of parasitic load in African children on cardiovascular fitness[219], and was recently validated in a systematic review calculating $VO2_{max}$ using direct oximetry and also a portable gas analyser[220]. The feasibility and acceptability of heart rate monitoring using wearable wrist (Fitbit Charge, UK) and chest-based (Polar, UK) heart rate monitors during exercise was also explored[221].

3d. *Blood pressure* (BP) was measured at rest using a manual sphygmomanometer (Medisave, UK). The median of 3 readings was used for both systolic and diastolic blood pressure. Blood pressure was also measured immediately after the shuttle run test and 5 readings were recorded. The difference between the 1st and 5th readings were then calculated to give a measure of recovery.

3e. *Haemoglobin* was measured (Hemocue) by a finger prick test. This was a potentially important contributor to cognitive outcomes and physical fitness[222].

Figure 3-7 SAHARAN Toolbox physical measurements

SAHARAN field body composition and physical function measurements. a: Subscapular skinfold thickness, b: Handgrip strength, c: Broad jump, d: Shuttle run test, showing Bluetooth speaker and measuring tape.

Caregiver questionnaire

A detailed caregiver questionnaire was also administered by a second data collector in parallel with the child measurements. The caregiver questionnaire measured household demographics, previous adversities, nurturing and contemporary factors associated with child growth and function.

	MARKER	MEASURE	Main outcome	Additional outcomes	RATIONALE
Caregiver questionnaire (90 mins)	Demographics	Household composition	Main caregiver	Years of schooling, household demographics, caregiver education	Household composition & caregiver education
	Socioeconomic status	SES score	Overall score	-	Socio-economic status
	SDQ	Socioemotional function	SDQ total score	SDQ subtest score	Behaviour
	Schooling & COVID impact	School engagement & attendance	Years of schooling	Attendance Alternative learning	Education
	Washington Group Child function module (WG)	Disability screening, including vision and hearing	Overall score	Hearing, vision, mobility problem subscale	Child functional abilities
	Child adversity scale	Adversities	Overall score	-	Measure of accumulated adversities
	Child parent relationship scale	Caregiver's relationship with child	Overall score	-	Nurturing
	MICS Child discipline score	Caregiver's relationship with child	Overall score	-	Nurturing
	EPDS	Maternal depression	Overall score	-	Depression
	HFIAS, HDDS	Food insecurity	HDDS score HFIAS score	-	Food insecurity
	HWISE, Water access	Water insecurity & access	HWISE score,	water volume	Water insecurity
	Gender norms (main study only)	Primary caregiver attitudes	Overall score	-	Caregiver capabilities
	Caregiver social support (main study only)	Primary caregiver attitudes	Overall score	-	Caregiver capabilities
	HIV questionnaire (main study only)	HIV status	ART for caregiver and child	TB treatment	

Table 3-4 Caregiver questionnaire sections.

MICS: Multi-indicator cluster survey (UNICEF), EPDS: Edinburgh postnatal depression score, HFIAS: Household Food Insecurity Assessment scale, HDDS: Household Dietary Diversity Scale, HWISE: Household Water Insecurity Experiences Scale, ART: Anti-retroviral therapy. Note that gender norms, caregiver social and a HIV questionnaire were included in the main study only. From[12]

Demographics related to household composition including number, religion, leadership[223] and primary caregiver education[224]. *Socioeconomic* *status* was measured using a wealth index previously developed for the SHINE study[225]. *Schooling exposure* and *COVID impact* were also asked. Both during the pilot and main study, COVID lockdowns occurred for primary schools. *The Washington Group / UNICEF Child Functioning module*[154,226] provided a screening tool for caregiver-reported functional difficulties in vision, hearing, vision, mobility, communication, learning, behaviour and emotions using a rating scale. *The child adversities index* screened for major life adversities since birth associated with reduced child development[227,228]. These questions were carefully piloted and selected to provide insight into adversity, whilst recognising this was a region with minimal social services support. Key elements of nurturing were measured using the Child-Parent Relationship scale[229] and the MICS Child Discipline questionnaire[230,231]. Caregiver depression was measured using local translations of *The Edinburgh Postnatal Depression score*. This had been validated and extensively used in this region and the SHINE cohort[232]. Food insecurity was measured using the *Household Food Insecurity Assessment Scale* (HFIAS)[233] and household diet using the Household Dietary Diversity Scale (HDDS)[234]. Water insecurity was measured using the *Household Water Insecurity Experiences Scale* (HWISE)[235].

Data Management

The vast majority of the SAHARAN questionnaire and observation data was collected with password-protected Android tablets (Samsung Galaxy Tab A) using the Open Data Kit (ODK) platform (https://opendatakit.org/). The ODK forms were programmed with expected data ranges and skip patterns. In addition there were free text sections to report any issues with data collection or other concerns such as child disability. Back-up paper forms were also provided in the field in case of a problem with the tablets. New data were manually checked by the Field Data Officers and / or Project Lead before being uploaded onto an ODK Aggregate Server, and stored on an SQL Server database at the end of each working day. All data were entered and stored using a unique participant identifier (PID) to maintain confidentiality.

The SAHARAN toolbox was then extensively piloted in 80 children and their families, including detailed cognitive and anthropometry standardisation. Within the pilot study of 80 families, the impact of COVID and coping strategies for education formed the basis of a separate publication[192]. The key results from the pilot are briefly described in this chapter and have been published elsewhere[192].

3.6 The SAHARAN Pilot study

The construct validity and internal consistency of the SAHARAN test battery were assessed by performing a cross-sectional pilot study on 80 children aged 7 years[192]. These children were randomly selected from 157 eligible children identified by community health workers in the Makusha (peri-urban) and Zvambande (rural) wards of Shurugwi district. Inclusion criteria included the child being aged 7 years, not being in the SHINE trial and having a primary caregiver who could provide informed consent. Detailed results are published elsewhere[192], although a short summary is also provided.

All children completed the full battery of SAHARAN tests in one visit, and the tests were shown to be feasible, acceptable and enjoyed by the child. Associations between different tests were explored within growth variables, and then similar physical and cognitive function domains (convergent validity) using least squares regression[192]. For the pilot, the physical function test results were standardised and added together to make a total physical score (TPS).

Pilot growth and physical function results

The association between HAZ or WAZ and body composition and physical function tests were explored[192] (Figure 3-8). Skinfold thickness plausibly increased with weight, although not with height or lean mass index (Fig 3-8 a-c), suggesting a prioritisation of body fat. Lean mass index increased with both height and weight and was associated with total physical function (Fig 3-8 d-f). Physical function was associated with lean mass, and height but not with BMI or fat mass (Fig 3-8 f-h), suggesting the importance of body composition for physical function.

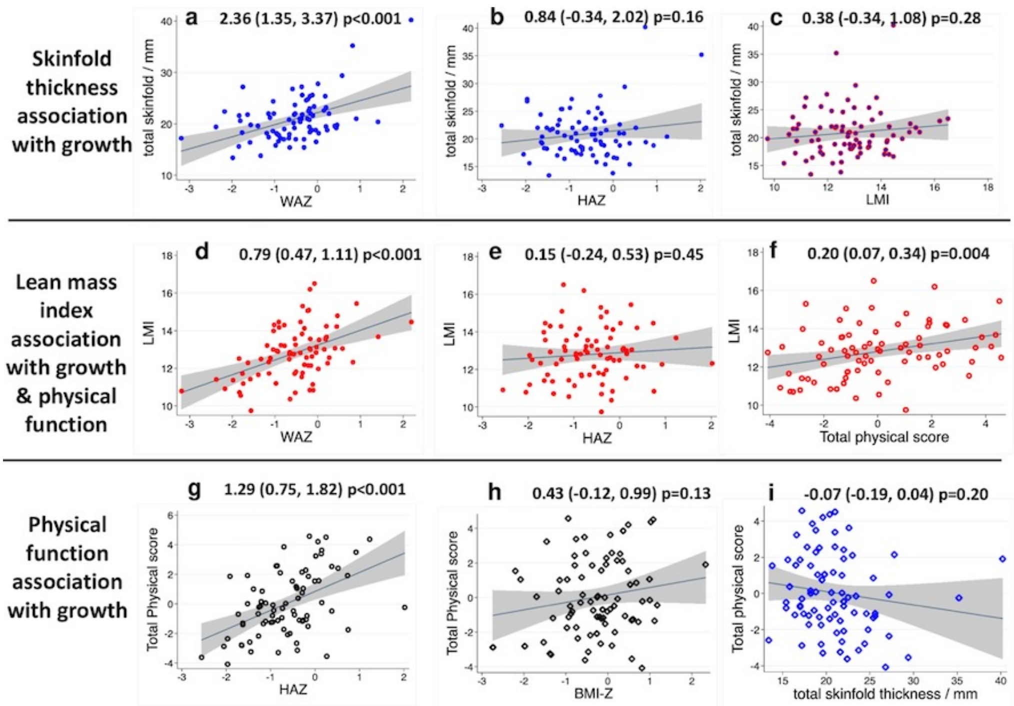


Figure 3-8 Pilot SAHARAN results for growth and physical function

Pilot SAHARAN toolbox results describing growth, body composition and exploring their association with physical function. (a) Total skinfold thickness was strongly associated with Weight-for-age Z-score (WAZ) since fat mass increases with weight. (b & c): Total skinfold thickness was not associated with Height-for-age Z-score (HAZ) or lean mass index LMI. (d): Lean mass index (LMI) was highly associated with WAZ, due to increasing lean mass with weight. (e): LMI was not associated with HAZ as LMI adjusts for the contribution of height to lean mass. (f): Total physical score (TPS) was strongly associated with LMI showing the positive contribution of lean mass to physical function independent of height. (g): Total physical function score (TPS) was highly associated with increasing HAZ, as lean mass increases with height. (h): TPS was not associated with Body Mass Index Z-score (BMI-Z) because of differing contributions from both fat and lean mass.(i): TPS was not associated with skinfold thickness. From[192]

Pilot cognition results

For cognition, the association between growth, years of schooling, or the child's perceived socioemotional support score were explored as exposures on each cognitive outcome (MPI, school achievement test, SDQ, and fine motor score). The association between each of the main cognitive measures were also explored to examine internal consistency, since each measure represented different domains of cognitive function. For the pilot, direct measurements of cognition showed internal consistency (Figure 3-9 a-b,): The Mental Processing Index (MPI), which provides a total cognition score from the KABC-II, was strongly associated with the SAT (Figure 3-9a) and weakly associated with fine motor skills (Figure 3-9b).

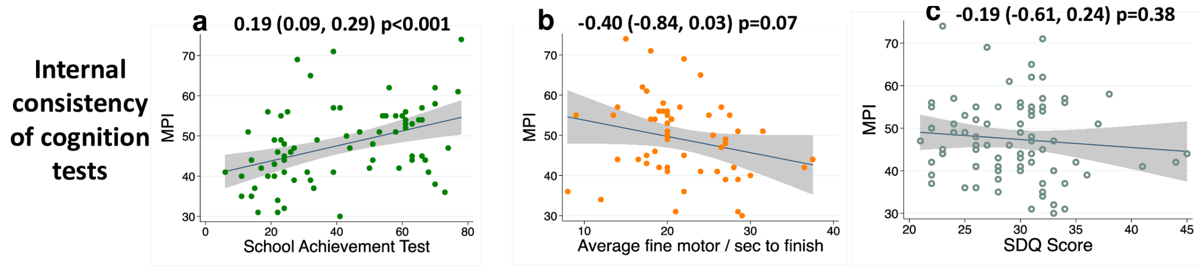


Figure 3-9 Pilot SAHARAN toolbox results for cognition

Pilot SAHARAN toolbox results describing cognition results and exploring their association with growth. (a-c): Internal consistency showed MPI (Mental processing index) was associated with increasing School achievement test (SAT) and faster fine motor completion time but not with strength and difficulties (SDQ) score from[192]

Socioemotional function as measured by the caregiver-reported SDQ was only weakly associated with SAT and not with MPI (Fig 3-9c) or fine motor function. In the pilot, there was strong evidence that each additional year of schooling was associated with the SAT, and weak evidence for a relationship with the MPI; there was no association with fine motor speed or SDQ score[192]. The child's perceived socioemotional support questionnaire was strongly associated with the SAT, and there was weak evidence for a relationship with the MPI score; there was no relationship between the child-reported socioemotional score or the caregiver-reported SDQ[192] (Figure 3-10).

Significant associations observed with the pilot data were summarised in Figure 3.10, which informed approaches to the main dataset (see chapter 4).

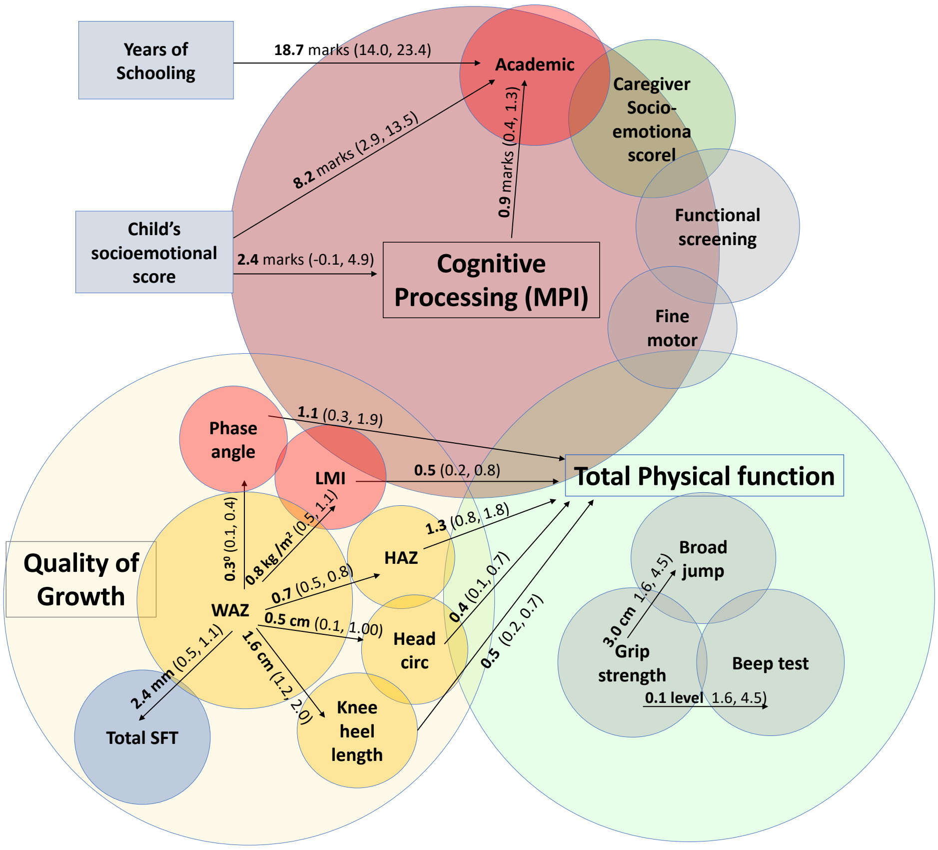


Figure 3-10 Associaitons for the SAHARAN Pilot

Significant associations within the SAHARAN toolbox between quality of growth, total physical function and cognitive function domains. Linear regression coefficients and confidence intervals are shown. Total SFT (total skinfold thickness), head circ (head circumference), LMI (lean mass index), HAZ (Height-for-age Z-score), WAZ (weight for age Z-score) from [192]

Overall the pilot SAHARAN toolbox showed significant associations between individual growth measures, which were strongly related to physical function (Fig 3-8 & 3.10). Cognitive function measurements showed internal consistency (Fig 3-9) and significant associations with schooling exposure and child socioemotional score(Fig 3-10)[192]. This helped to demonstrate content and face validity, acceptability and internal consistency. The standardisation performed during the pilot study also demonstrated acceptable inter- and intra-rater reliability. Concerns were raised for two of the KABC-II subtests during the pilot. Adaptation of some subtests within the KABC-II is described next and has been published elsewhere[236].

3.7 Adaptation of the KABC-II for improved cross-cultural validity

Introduction

Using the Luria model, the 8 KABC-II subtests selected are divided into 4 cognitive domains: i) Story Completion and Pattern Reasoning subtests provide the Planning domain for reasoning; ii) Atlantis and Atlantis Delayed subtests provide the Learning domain, which measures short and long-term memory; iii) Number Recall and Word Order subtests encompass the Sequential domain, which measures sequential memory; iv) Rover and Triangles subtests provide the Simultaneous domain, which combines logic and problem-solving[190] (see Figure 3.12b). To perform each subtest successfully, a certain level of baseline understanding within the child should be achieved. The SAHARAN pilot study noted that the first 50 children were scoring relatively poorly on the story completion and pattern reasoning subtests. The concern was that this poor performance may result in a skewed measurement of reasoning.

Whilst KABC-II has been widely used across Africa, there has been little documented pre-testing and piloting exploring individual subtests' cross-cultural validity in different contexts. For story completion, children pick the missing picture(s) from a selection of pictures to complete a picture-based story by aligning them in the correct sequence. For the pattern reasoning task, children have to select the correct printed shape or image to fit within a repeating pattern[237]. The poor performance in both these subtests had previously been noted in rural South Africa[190]. Therefore 2 separate methods were used for the adaptation of cognitive subtests performed during this study (Fig 3-11): the first used substitution, addition and rearrangement of questions for story completion, the second including additional questions for pattern reasoning. Both were performed in collaboration with Professors Alan and Nadeen Kaufman (the original developers of the KABC-II) and Dr Tamsen Rochat.

A stepwise process was adopted, based on initial concerns on face validity and then subsequent monitoring as cognitive measurement continued (Figure 3.11). Analysis included subtest scores, individual question analysis and feedback from children to check their understanding of individual questions being asked.

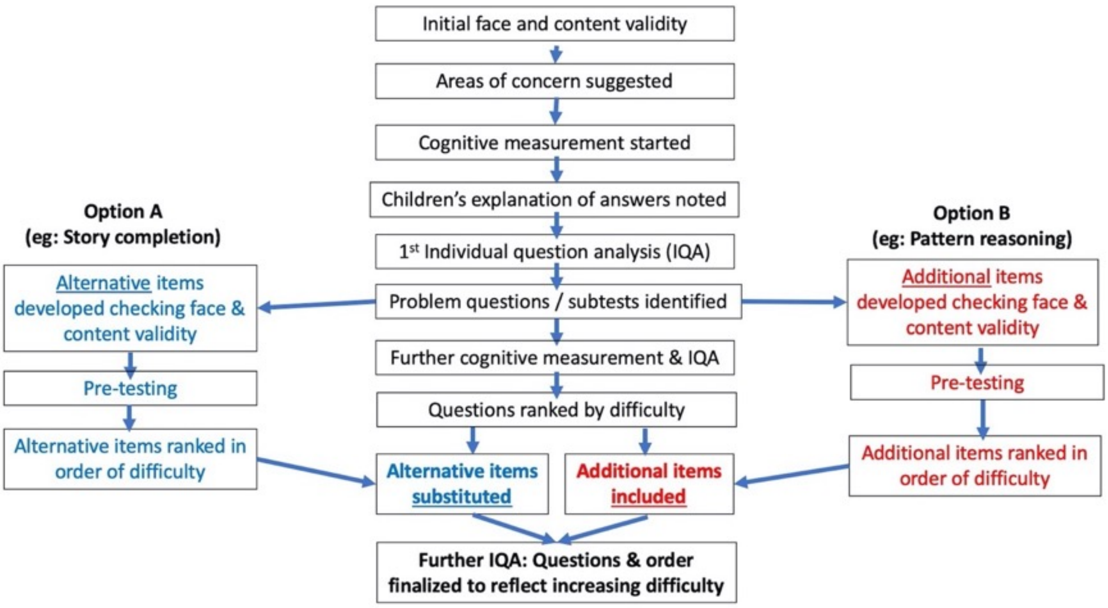


Figure 3-11 Stepwise process of KABC-II adaptation

Stepwise process of monitoring and adaptation used for cognitive measurement. Figure from [237]

Alternative items (story completion) or additional items (pattern reasoning) were then developed, printed and laminated. They were checked for face and content validity and were then pretested with other children before being included in the study. Custom scoring sheets were also developed. Data was analysed with Excel and Stata 15.0. We hypothesized that (a) the two modified planning subtests would increase significantly with modifications, thereby providing evidence that efforts to make the tests more culturally appropriate were successful; and (b) construct validity would improve with better correlations between the domains of the KABC-II for the adapted test[237].

KABC-II overall results

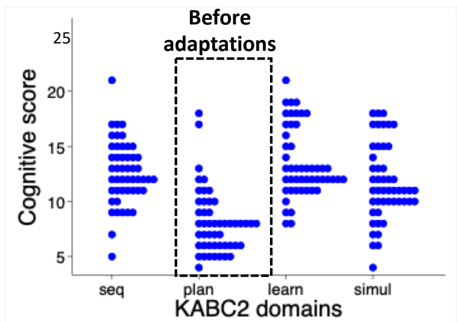
Analysis of the first 50 children showed that scores were negatively skewed, particularly in the planning domain, comprising story completion and pattern reasoning subtests (Fig 3.9 a & b). A post-hoc Tukey's test provided evidence that marks were lower for planning than the other 3 domains (Fig 3-12a): The planning domain had a mean difference of 5.4 marks lower (95%CI 3.8, 7.0; P<0.001), simultaneous (3.5 marks; 95% CI 1.9, 5.1; P<0.001) and sequential domains (4.6 marks; 95% CI 3.0, 6.2; P<0.001). For comparisons between the other domains, the simultaneous score was less compared to learning (1.9 marks; 95% CI 0.3, 3.5; P=0.01) only. There was no evidence of differences for sequential compared to learning (0.9; 95% CI -0.7, 2.5; P=0.5) or sequential compared to simultaneous (1.0; 95% CI -0.6, 2.6; P=0.34)[237].

Story completion

For story completion, on individual question analysis (IQA), it became clear that there were challenges with items 4, 6, 8 and 9 (Fig 3.12c). As in many cognitive tools, later questions in the KABC-II are designed to be more difficult. However, when asked to explain their choices, children did not sufficiently understand the picture stories on these items to answer them logically.

Alternative picture stories were designed, printed, adapted and pre-tested. These were designed to replace items 4, 6, 8 and 9. However, in pretesting, it became clear that the alternative stories were themselves of varying difficulty. Hence in discussion with Tamsen Rochat, the alternatives were re-ordered to place the remaining KABC-II questions in order of increasing difficulty (measured using the proportion of children who got them correct, Fig 3-12d). Item 6 was also rearranged to item 10. The proportion correct on each story completion item was calculated, both for the unmodified story completion and the adapted story completion version, which suggested an improvement (Fig 3-12d). Children scored significantly higher on the modified story completion (mean 4.8, SD 1.3, 95% CI 4.2, 5.4) than on the original story completion (4.1, SD 1.2, 95% CI 3.8, 4.4; Combined score 0.7, 95% CI 0.0 to 1.4, p =0.04). It is worth noting that numbers were lower for those asked on the modified questions (n= 10 to 20) than the original (n=50) as these modifications occurred within the pilot study[237]

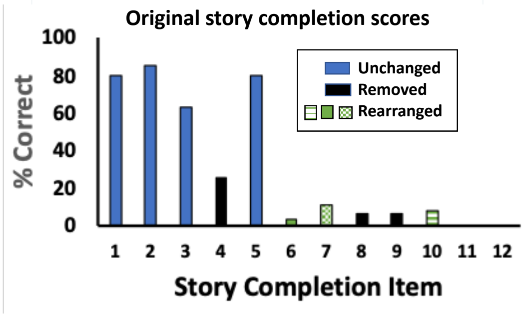
a



b

Sequential	Planning	Learning	Simultaneous
Number Recall	Story Completion	Atlantis	Rover
Word Order	Pattern Reasoning	Atlantis Delayed	Triangles

c



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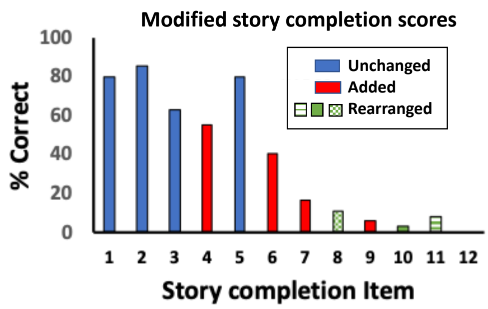


Figure 3-12 Initial KABC-II monitoring and story completion development

a: Scores for the first 50 children showing reduced scores in the planning domain, b: individual subtests and their cognitive subdomain, c: Individual question analysis showed items 4, 6, 8 and 9 scored poorly, d: Adaptation of story completion showing additions and rearrangement of items. Adapted from[237]

Pattern reasoning

For individual question analysis on pattern reasoning, it became clear that few children were getting correct answers after question 4 (Figure 3.13b). Discussion with community members and primary school teachers illustrated that children had not previously seen puzzles with alternating patterns. IQA confirmed that the single training question (item 2) which demonstrated alternating patterns in the original KABC-II was insufficient for children to grasp this consistently for further questions. Twelve additional questions with alternating patterns were developed and then pre-tested, and the 7 most appropriate questions were chosen to be included, based on face validity and feedback from the pre-testing[237]. On the advice of Prof Alan Kaufmann, all 7 additional pattern questions were included as training questions for every child and included in the scoring. This modified pattern reasoning was called "Pattern plus" to provide suitable experience and scoring of alternating patterns. We developed routine explanations for the Pattern Plus questions to standardise the training given to the child. 50 children had an initial score of 4.0 (SD 2.3; 95% CI 3.3, 4.6) and after training with Pattern plus, the subsequent 20 children scored 4.7 on the same KABC-II questions, (SD 1.9, 95% CI 3.9, 5.3). The mean increase of 0.7 marks was not significant (95% CI -0.4, 1.8, p=0.2, Figure 3.13b). However, when additional scoring of the pattern plus questions was included, the mean score increased significantly to 5.8,(SD 2.6, 95% CI 4.6, 7.0, p=0.005) (mean difference +1.8 marks, 95% CI (0.6, 3.1, p=0.005) as shown in Figure 3.13c[237].

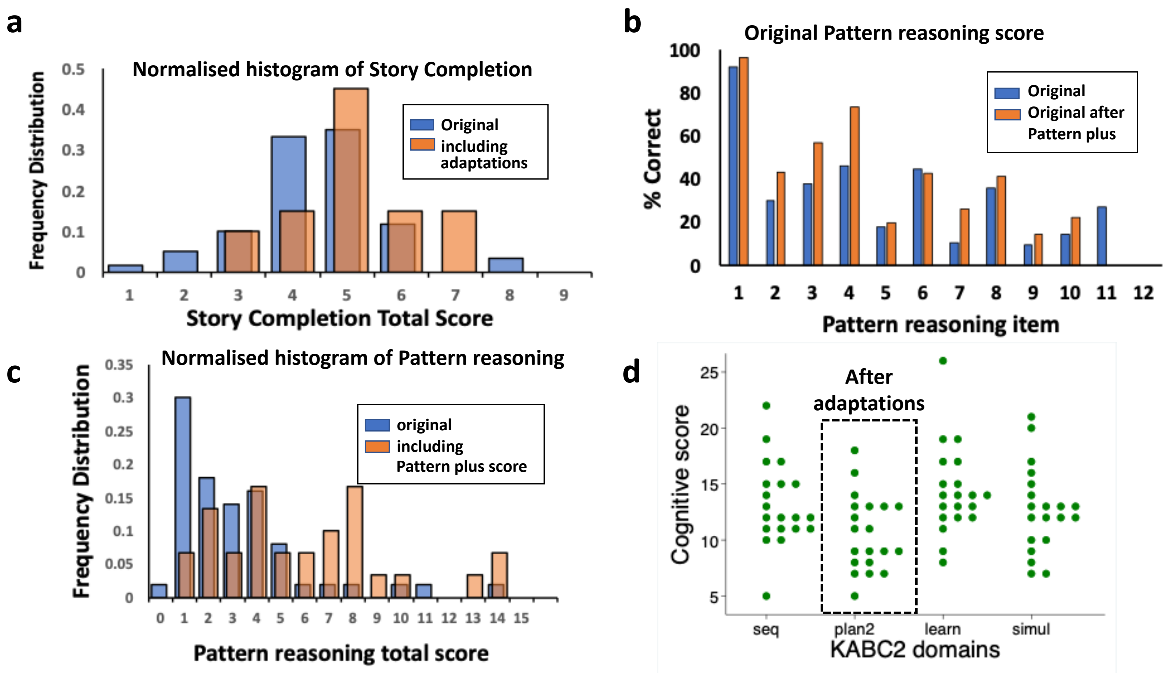


Figure 3-13 Development and analysis of KABC-II subtests

Further development and analysis of story completion and pattern reasoning subtests, a) Histogram of total scores for original and modified story completion, b) Scores for original pattern reasoning answers, before and after Pattern Plus training, c) Histogram of total scores for original and modified pattern reasoning, d) Scores for 20 children who did both modified story completion and pattern reasoning. From [237,238].

Standard KABC-II scaling by age was also applied to the updated Story completion and pattern reasoning subtest total. There was a significant difference in age-adjusted KABC-II scaled scores on the planning domain between the 50 children who had the unmodified KABC-II (mean score 8.1, SD 2.87, 95% CI 7.2, 8.9) and the 20 children who had both modified story completion and pattern reasoning (mean score 10.6, SD 0.75, 95% CI 9.0, 12.2). The mean difference was 2.5 KABC-II-adjusted marks (95% CI 0.9, 4.13, p=0.002). This suggested a beneficial effect of the modifications (Figure 3.13d)[237].

For the last 20 children who had the modifications, scores remained lower in the modified planning domain (mean score 10.6 (SD 3.4)), compared to the other domains (learning 14.3 (SD 4.0), sequential 13.2 (SD 3.7), simultaneous 12.7 (SD 3.8); P=0.001). However, a post-hoc Tukey's test demonstrated that marks were significantly lower only for planning compared to learning (mean difference 3.7 marks; 95% CI 0.7, 6.8), but not for sequential scales (2.6 marks; 95% CI -0.5, 5.7) or simultaneous (2.1 marks; 95% CI -0.5, 5.2). For these 20 children, there was no evidence of differences for comparisons between the other domains. The intraclass correlation coefficient (ICC) provided the opportunity to compare the variability between the KABC-II domains within the same children. For the first 50 children using the unmodified planning domain, the ICC was 0.43 (95% CI 0.13, 0.64). For the last 20 children using the modified planning domain it was 0.69 (95% CI 0.37, 0.87)[237].

Discussion on KABC-II adaptation

Two subtests within the KABC-II were successfully adapted to a rural, Sub-Saharan context using two complementary methods: substitution, addition and rearrangement for story completion and addition of further training questions for pattern reasoning. Both adaptations increased the scoring on these subtests, potentially partially correcting the reduced performance in the planning subdomain previously noted[239]. However, it is also plausible that children will continue to have lower scores in the planning subdomain due to cultural factors such as less exposure to these types of puzzle[239].

The increase in mean scores for both subtests provided some evidence the adaptations had made the subtests more culturally appropriate (15% increase in story completion, 30% increase in pattern reasoning). This was also suggested by the intraclass correlation coefficient (ICC) between domains also increasing with the adaptations, which indicated the variability between domains may have reduced with the modifications. The higher intercorrelations between planning and the other domains reflected by an increase in ICC suggests a potential improvement in construct validity of the planning domain. This is corroborated by the confidence intervals where the ICC before modification of 0.43 (95% CI 0.13, 0.64) excludes the ICC after modification of 0.69 (95% CI 0.37, 0.87). However it should be noted that the pre-modification value of 0.43 is included in the post-modification confidence interval of 0.37 to 0.87; therefore, inferences about construct validity are tentative and require cross-validation with a larger sample size[237].

The process of determining the face validity of items and then monitoring individual responses to questions empowered data collectors and the local community to monitor children's answers and suggest adaptations. This led to a more culturally inclusive tool[237]. The IQA also provided a way to confirm or refute initial concerns on face validity: for example, in story completion the fried egg cooking example was immediately flagged and eventually replaced (as rural Zimbabwean households boil or scramble but do not fry eggs, hence the pictures of the whitening of the egg with heat were not well understood). By contrast, the blowing balloons sequence was well understood by children, even though the long type of balloons in the pictures were not commonly seen. All the adaptations were discussed in detail with Professors' Alan and Nadeen Kaufmann, who originally developed the KABC-II in the USA and provided invaluable insight and encouragement. Similarly the adaptations were discussed in parallel with Dr Tamsen Rochat who has extensive experience of using the KABC-II in a Southern African setting[190,237]

The KABC-II adaptation process also had some limitations. Tukey's pairwise comparison test between domains does include an adjustment for multiple testing. However, comparing multiple subtests should be cautiously interpreted due to the increased risk of chance errors[237]. For our population of 7 year-old children, no child went beyond item 12 on story completion (the tyre splash story), so this was where our adaptation finished. Therefore, for studies using the KABC-II in older children in rural Sub-Saharan Africa, a similar monitoring phase for later items is recommended to highlight any problematic questions and then pretesting of any alterations. The number of children asked on each new story completion item also varied in total, as these items became available at different time-points and some children reached the discontinue rule before completing all questions. The use of photographs in story completion as an alternative to illustration may also change some cognitive processing of the task, so ideally imaging software should be used to convert items to illustrations. For younger children, the addition of seven pattern plus questions may be too many, and so similar adaptations may use fewer and simpler patterns (Gladstone, personal communication). The process of developing, printing and pretesting alternate or additional items took time so that more children were tested before the adaptations (n=50) than for story completion modifications or pattern plus (n=20). Finally, test re-test reliability was not measured because it was not possible to revisit the children due to the rural locations and cross-sectional nature of the pilot study, although this step is generally recommended to demonstrate stability of any tests or modifications[237].

This piloting showed that substitutions, rearrangements and additions of items can improve the cross cultural validity of these subtests by working in collaboration with the original developers, local community and participants[237]. The next stage was to scale up the SAHARAN toolbox with the KABC-II adaptations by recruiting further data collectors and final adaptations before performing it in the SHINE cohort.

3.8 Main SHINE follow-up study

Study refinements following the pilot

For the SHINE Follow-up study, the majority of techniques and measurements were the same as the pilot study described earlier. Additional measurements included the supra-iliac skinfold thickness, to provide a second measure of central subcutaneous fat to complement subscapular skinfold thickness. In addition, blood pressure was measured 5 times approximately 1 minute after completing the shuttle run test, to provide further information on the trajectory of recovery. Pictorial records of effort for the physical function tests were removed as they were not useful in the pilot and only showed a moderate correlation with more objective methods used[240]; they were replaced with sections in the ODK form where the DC flagged any poor effort for physical function tests. For the caregiver questionnaire, two further sections on the psychosocial characteristics of caregiving ability were added; these were defined as caregiver capabilities and have been previously investigated in early-life in the SHINE cohort[140]. More equitable gender norm attitudes and improved support from friends, neighbours and relatives were associated with increased early-life growth[241]. In addition, an HIV questionnaire was also included which asked about the caregiver's and child's HIV status, Anti-Retroviral Therapy (ART) use, and treatment for tuberculosis. This section also included results from HIV testing where appropriate.

Community sensitisation and training

For the main study, sensitisation sessions and CHW training were conducted via all clinics in Shurugwi district. Four further DCs were recruited and trained in research ethics, data management and the techniques described above. They were then paired with an experienced DC from the pilot and supported with additional supervision for the initial 10 visits. A specific field data officer was also recruited and trained to provide visit coordination, data management and checking of completed ODK forms. In addition, 8 additional research nurses coordinated visits with the 197 CHWs across the district. Due to COVID lockdowns, disruptions and quarantine periods within the team, these 8 additional nurses were additionally trained in consent and performing the caregiver questionnaire only. This enabled multiple catch-up visits to be performed when COVID caseload was low.

Pre-screening and Verification

In a similar model to the pilot, the CHW was given a pre-screening form with details of the household and child previously in the SHINE trial, to ascertain if they were interested in participating in the SHINE Follow-up study. When pre-screening was successfully completed and the household was interested, a mutually convenient date for the household, CHW and research team was agreed. The CHW then introduced the 2 DCs to the household, who then confirmed it was the original SHINE child and primary caregiver that were present, using a pre-populated screening form. Wherever possible information from the SHINE database was matched with written records (eg birth certificate, child health card). Evidence was also noted of previous SHINE study involvement (eg old consent forms or a SHINE latrine visible in the household). A pre-defined decision tool assisted with any mismatch of details, with phone-based back-up as required. One or two tents were pitched in or close to the household after both DCs verified that this was the correct child. SHINE households were single-family dwellings that were typically surrounded by subsistence farmland. The DCs ensured the tents were sufficiently isolated for confidentiality during informed consent and data collection (the mean distance between houses in SHINE was 82.6m[73]). For children who had moved to peri-urban settings, assessments were performed nearby in vacant land, or occasionally at the research hub. Similar to the pilot, written informed consent was obtained from the primary caregiver, and written assent from the child where possible. Additional details included in the SHINE consent form were consent for HIV testing and consent for additional visits in the future for health monitoring and annual assessments.

HIV testing and referrals

For the SHINE follow-up study, HIV testing was offered to all caregiver-child pairs to ensure that an updated HIV exposure status was determined. This was in case of maternal incident HIV infection and / or child infection due to prolonged breastfeeding after the 18-month trial endpoint. HIV testing was not performed if the caregiver refused testing, had a documented negative HIV result in the previous 3 months or were already known to be living with HIV. A sealed envelope was opened at the end of the SAHARAN toolbox measurements so that all assessments had been performed whilst the data collectors were blinded to the caregiver and child HIV status.

If the mother was tested as HIV-negative, then the child was not tested. For mothers who declined testing, were living with HIV or were not available, the child was offered HIV testing with age-appropriate assent using role-plays. Research nurses were trained in these assent role plays by specific trainers from the Zimbabwean Ministry of Health and Child Care. Determine rapid tests (Abbott) were used for initial testing; positive results were repeated with the Stat-Pak rapid test (Chembio). Dried blood spot (DBS) testing was an alternative option offered for participants who preferred not to be tested in real-time in the homestead. Referrals were made to local clinics for positive HIV results, to initiate ART and cotrimoxazole. Referrals were also made for any child or caregiver who appeared unwell, had high blood pressure or was very underweight, or was disabled and not known to the local clinic. Any caregiver mental health or child welfare concerns were discussed with the Project lead and Shurugwi hub manager and followed up by the District Health Executive.

Trial oversight and registration

The Medical Research Council of Zimbabwe (MRCZ) approved the study protocol for the SHINE follow-up study (8th February 2021, MRCZ/A/1675) as amendments to the main SHINE trial protocol. Additional amendments were also approved by MRCZ for the main study (6th April 2021, 25th June 2021 and 4th November 2021). During the interventions in SHINE, there was an independent data and safety monitoring board comprising of 2 Zimbabwean physicians and a statistician based in the UK, who reviewed interim adverse event data in the main trial from enrolment to 18 months of age. However, for the SHINE Follow-up study, this was not required since no interventions were provided after 18 months of age. The Zvitambo Institute for Maternal and Child Health Research compliance department performed regular visits to check on trial reporting, consent processes and protocol deviations. The SHINE follow-up study was also registered with the Pan-African Clinical Trials Registry (PACTR202201828512110), available at https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=16147

Validation and quality control.

Several validation and quality procedures were applied. Supportive supervision was provided by the project lead with monitored field visits every week, and additionally the study clinician (JP) observed complete visits with all data collectors every 3 to 6 months, as well as the first 30 visits of the SHINE Follow-up study. In addition, some neurocognitive assessments were video recorded to provide additional monitoring. The data collectors underwent refresher training and performed a standardisation week every 9 months. The 8 Data collectors (DCs) were divided into 2 groups of 4 for the whole standardisation week. For each day of standardisation, measurements were performed simultaneously on 2 children in separate households, 1 for each group of 4 DC's. One DC performed the KABC-II on a SHINE child, and 3 others marked the KABC-II independently. The DCs then swapped each day over four days, so that each DC was observed to perform the KABC-II and all

DCs marked independently. A similar process for the SAT and timing for the finger tapping was also performed, with monitoring at all times by an independent researcher to ensure independent marking. At the end of the week, the inter-item correlation matrix between DC's was compared to see if any DC's correlated poorly with the other DC scores. The absolute value of the 2-way mixed intraclass correlation (ICC) for average measures was calculated for each team of 4 DC's, using SPSS v25. Scores were broadly similar with inter-item correlation >0.99 between DC's. The 2-way mixed ICC value between data collectors was also >0.99 for the scoring of the KABC-II and SAT, as well as for the timing of finger tapping.

The Plus-EF could not be performed in this way since the results from the child were directly recorded by the tablet. Similarly the Strengths and Difficulties Questionnaire (SDQ) and child socioemotional score were both from a caregiver questionnaire so unsuitable for standardisation. For physical function measurements, standardisation was not performed because the grip strength was recorded digitally. Similarly, the shuttle run test and broad jump distance could only be directly measured by the data collector performing the test, without independent assessment by other DCs.

For key anthropometric measurements, the intra-observer technical error of measurements (TEM) was calculated by finding the deviation between an operator's individual measures on the same child between the morning and afternoon measurements, using this calculation[242]

$$TEM = \sqrt{\frac{\Sigma(x_a - x_p)_i^2}{2n}} \tag{3.1}$$

Where x_a *is the morning measurement and* x_p *is the afternoon measurement by the same DC on the same child. N = number of children measured, i= number of differences and* Σ is the *sum of differences.*

The differences were then squared and summed between all the children measured, dividing this by the number of children multiplied by 2, and then applying the square root.

The inter-observer TEM was also calculated across all measurements as a comparison using this equation[243] (eq 3.2).

$$TEM = \sqrt{\left(\frac{(\Sigma_1^N (\Sigma_1^K M^2) - \frac{(\Sigma_1^K M)^2}{K}}{N(K-1)} \right)} \quad (3.2)$$

Where N is the number of individuals measured (eg 8 children), K is the number of data collectors (eg 8 DCs) and M is the measurement.

The relative TEM (%) was also calculated to enable comparison of technical error between the measurement methods used[243] (Eq 3.3)

$$Relative\ TEM = \left(\frac{TEM}{Mean}\right) \times 100 \quad (3.3)$$

Sample results of TEM for the first standardisation are demonstrated below:

Anthropometry Variable	Mean value	Inter-rater TEM	Relative TEM, %	DC Intra-rater Technical Error of Measurement (TEM)							
				1	2	3	4	5	6	7	8
Height, cm	120.4	0.1	0.1	0.3	0.5	0.7	0.6	0.2	0.2	0.3	0.0
Head circumference, cm	50.6	0.2	0.3	0.3	0.6	0.5	0.5	0.3	0.2	0.6	0.2
Triceps skinfold, mm	6.3	0.2	3.2	0.5	0.8	0.7	0.0	0.1	0.0	1.4	0.5
Calf skinfold, mm	10.0	0.2	2.1	0.4	1.1	1.2	1.0	0.6	0.6	1.4	0.7
Subscapular skinfold, mm	5.0	0.2	3.4	0.6	0.5	1.1	0.5	0.3	0.5	1.2	0.4
Supra-iliac skinfold, mm	5.7	0.2	4.4	0.5	1.6	2.1	0.7	0.4	0.5	1.2	0.6
leg length, cm	36.7	0.1	0.3	0.2	0.5	0.2	0.1	0.3	0.5	0.4	0.1

Table 3-5 Results from the first anthropometry standardisation

Results from the first anthropometry standardisation showing mean value of measurements, inter-rate technical error of measurement (TEM), relative TEM and intra-TEM for each of the 8 Data collectors (DC's).

Comparing the TEM with the ChroSAM study standardisation showed a similar level of precision which was reassuring[242], although the SHINE follow-up study (SFU) had no gold standard for comparison. The measures selected demonstrated use of all the different types of anthropometry equipment used. There was greater intra-technical error of measurement (TEM) noted for the skinfold thicknesses, particularly for the calf and supra-iliac skinfolds. Data collectors who showed higher values of TEM for specific measurements (eg supra-iliac skinfold and height for DC3) were supported with additional training and monitoring.

Sample size and child selection

The primary outcome was pre-defined as the KABC-II total neurodevelopmental score, called the mental processing index (MPI). Among all children evaluated at the trial endline at age 18 months, 250 per intervention arm meeting the eligibility criteria were randomly selected by computer using the *sample* program in Stata 13. In brief, the eligibility criteria were all children measured who were aged 7-8 years, still resident in Shurugwi district, and born to mothers without HIV who were willing to provide written informed consent. Children who were no longer resident in Shurugwi, with an unknown maternal pregnancy HIV status, or outside the age window were ineligible. Children who were unable to be visited or whose family declined participation were replaced randomly by another eligible child from the same trial arm.

The SHINE 2x2 factorial trial design enabled the evaluation of the IYCF and WASH interventions as two trials run in the same population, stratified by maternal HIV status[12]. For the analysis of IYCF as the primary outcome, the two IYCF-containing trial arms were combined (IYCF alone, and IYCF+WASH) and compared to the two non-IYCF arms (WASH alone, and standard-of-care). This primary analysis was unadjusted. Hence, 1000 children born to mothers without HIV (500 IYCF vs 500 non-IYCF) were assessed. This provided 86% power to detect a 0.2 standard deviation difference in (MPI) between IYCF and non-IYCF arms with alpha 0.05, assuming sampling from 100 clusters and intra-cluster correlation of 0.05[12]. This allowed the exploration of the difference in IQ scores observed which was similar to those observed at 3-7 years of age among children followed-up in the INCAP study[5], and was also the approximate magnitude of benefit in socio-emotional scores in a small-quantity lipid-based nutrient supplement (SQ-LNS) trial[106]. No adjustment for loss to follow-up was required because data collection was undertaken directly after consent and enrolment. For the analysis of WASH as a secondary outcome, the two WASH-containing trial arms (WASH alone, and IYCF+WASH) were combined and compared to the two non-WASH arms (IYCF alone, and standard-of-care). Hence the SHINE 2x2 factorial design also enabled 500 WASH versus 500 non-WASH children to be assessed[12].

For children born to mothers living with HIV (MLWH), the target sample size was 300 (of which 273 were enrolled and measured). This allowed exploration of the impact of HIV exposure on child growth and function as a secondary outcome (Chapter 6).

Definition of disability

The Washington Group UNICEF tool was used for screening, and then confirmed with clinical notes from the team recorded on the child questionnaire. For disability screening, a definition of 'functional difficulty' was made for any answer that recorded "a lot of difficulty" in sight, hearing, walking, self-care or communication. A definition of 'severe functional difficulty' was made for any answer with "cannot do at all" in sight, hearing, walking, self-care or communication. Similarly, a child was defined as having learning difficulties or severe learning difficulties if the caregiver reported "a lot of difficulty" or "cannot do at all" for questions that asked if the child had difficulties in learning or remembering.

Definitions of disability were then confirmed by examining all additional comments recorded by the data collector. As part of training, data collectors were taught to record any additional disabilities in the comments section of the case report form (CRF). For physical disability, the comments of the data collector also determined whether the child was excluded from specific physical function tests due to specific problems (eg asthmatic so shuttle run test not performed). Acute injuries were not classed by the WG UNICEF tool as affecting function if they did not cause long-term disability. Disability was defined by either the WG UNICEF tool responses or the qualitative comments by trained nurses. Some children's disability status in the visit notes did not reflect the answers in the WG UNICEF tool. The inaccuracies within the coding of disability for the WG UNICEF tool meant that further analysis of function was not possible using the WG UNICEF scoring, so this secondary outcome was not analysed in further detail.

Child number for children born to mothers without HIV	WG UNICEF scoring				Definition	Further explanation from Data Collector notes
	Functional difficulty	Severe Functional difficulty	Learning difficulty	Severe learning difficulty		
C1	0	0	1	0	Cognitive disability	Delayed milestones & syndromic
C2	1	1	0	1	Cognitive disability	Severe disability, microcephaly
C3	1	1	1	0	Cognitive disability	Child disabled
C4	0	0	0	0	Cognitive disability	Disabled child & syndromic
C5	0	0	0	0	Cognitive disability	Cognitive disability
C6	0	0	1	0	Cognitive disability	Child disabled & unable to understand
C7	1	1	0	0	Cognitive disability	Child disabled and chronic condition
C8	1	1	0	0	Cognitive disability	No recorded comments but DC reported disabled
C9	1	1	0	1	Cognitive disability	Child disabled and unable to talk
C10	0	1	0	1	Cognitive disability	Syndromic child not speaking
FT1	0	0	0	0	Fine motor disability	Unable to grasp finger tapping
FT2	0	0	1	0	Fine motor disability	Child not concentrating for finger tapping
FT3	0	0	0	0	Fine motor disability	Unable to do finger tapping
SRT1	1	1	0	0	Shuttle run disability	Asthmatic child
SRT2	0	0	0	0	Shuttle run disability	Leg length discrepancy
SRT3, BJ1	0	0	0	0	Shuttle run & broad jump disability	Asthmatic child

Table 3-6 Definitions of disability using both WG UNICEF screening tool and clinical comments by the data collector for children born to mothers without HIV

Statistical analysis plan

Further detail was described in the statistical analysis plan (SAP) uploaded prior to unblinding at https://osf.io/w93hy/. Reporting of results followed the guidelines established in the extended CONSORT guidance for cluster-randomized trials[244]. Further details of statistical methods are presented in each of the results' chapters 4 to 7.

4 Chapter 4: SAHARAN Toolbox results within the SHINE Follow-up Cohort

4.1 Introduction

Hypothesis tested

This chapter tests the hypothesis that growth up to school-age and contemporary factors have strong associations with school-age cognitive and physical function.

SHINE Follow-up measurements

School-age has historically been termed the 'missing middle' due to a lack of studies and tools to assess this area period. The School-age Health, Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox was developed to measure school-age growth, body composition, cognitive and physical function (Chapter 3). There has been less focus on school-age health and functional outcomes (5-14 years), particularly in low- and middle-income countries (LMICs), since routine health information systems provide little monitoring for this age group [245]. Mortality at age 5-14 years is considerably higher in LMICs compared to high-income countries (HIC's), particularly within sub-Saharan Africa[246]. Beyond survival, child growth and developmental trajectories after 5 years are rarely measured[100]. Recent studies have suggested across the globe that contemporary social, nutrition and environmental factors affect school-age height and BMI[103]. Investigating school-age health outcomes may expand the timing of effective interventions to address growth, physical, cognitive, and socioemotional development in LMICs[104].

It is widely accepted that the contemporary environment continues to influence child growth and development in multiple ways[247]. For example, food security[248], adversity[249], caregiver support[250], nurturing care[251] and schooling exposure[252] may all be associated through multiple mechanisms with school-age child growth and function.

The enrolment into SHINE Follow-up (SFU) first describes the randomisation and loss to follow-up within the broader SHINE cohort. Results for individual tests are compared with other cohorts where possible to check their applicability and validity. This chapter then explores the following contemporary exposures:

1) Impact of child sex
2) Correlations between individual tests within the domains of cognition, physical function and growth, to test internal consistency (as described in chapter 3).
3) Association of growth up to school-age on school-age function
4) Principal components analysis (PCA) of SAHARAN outcomes
5) Hierarchical clustering using the PCA of SAHARAN outcomes
6) Associations of contemporary environmental exposures with the PCA of the SAHARAN outcomes

It presents the results from SAHARAN toolbox assessments in 1000 school-age children born to mothers living without HIV who were previously in the SHINE trial.

4.2 Methods

Children were re-enrolled from each intervention arm of the original SHINE trial (including the standard of care arm). The protocol, trial design, and statistical analysis plan for the SHINE follow-up study have been described in Chapter 3 and are also available[12] at https://osf.io/w93hy/.

As previously described (Chapter 3), the SAHARAN toolbox consists of a caregiver questionnaire, child questionnaire, and direct tests undertaken with the child to assess cognitive function, growth and physical function[192]. Assessments were performed by primary care nurses extensively trained and supervised in the study measurement techniques, during a single home visit using two tents pitched in or close to the household.

Statistical analyses

Results from the SHINE follow-up study (SFU) were compared with cohorts from comparable contexts that had undergone measurements using similar tools, using published means and standard deviations where available. This was to examine the plausibility of the SFU results. Some of these results were found from publications from research teams that supported the SAHARAN training remotely, such as the Siyakhula cohort for the KABC-II [190] or from Jamaica for fine motor tapping[173]. Others were available through publications linked to the tools[253] or techniques[219,254,255].

The impact of child sex on SAHARAN toolbox outcomes were explored by first calculating the mean and SD for each sex. The effect of child sex was then explored using generalised estimating equations (GEE) that account for within-cluster correlation to estimate effect size, with an exchangeable working correlation structure. The first model was unadjusted. In the second model, adjustment was made for SHINE trial arm only. In the third model trial factors (study nurse / data collector, ambient temperature, calendar date of measurement, child sex, and exact age) were included in addition to trial arm.

Reliability was also assessed by measuring the internal consistency of outcomes (Chapter 3) across cognitive functional domains. This was compared by correlation analyses, including the primary outcome of the mental processing index (MPI, which was the age-scaled KABC-II total score) and other secondary cognitive outcomes. Similarly, consistency between physical function outcomes and then growth measurements were assessed by correlation analyses.

4.2.1.1 *Effect of growth on function*

The effect of child growth by school-age on functional outcomes was explored using GEE to estimate effect size, with an exchangeable working correlation structure. The initial GEE models were unadjusted for other covariates. In the first model, adjustment was made for SHINE trial arm only. In the second model trial factors were included.

A third more detailed model examining the impact of growth by school-age on function was also derived using a Directed Acyclic Graph (DAG) developed using DAGitty (https://dagitty.net) before analyses were performed. DAGitty is an online graphical tool that enables causal diagrams to be constructed for minimising bias in epidemiologic studies[256]. For the final model, selected covariates were entered into a multivariable regression model based on the DAG's adjustment for a direct effect (Figure 4-3) in addition to trial factors. Hence DAGs provided a method for selecting which confounders to include for adjusted models. For this third adjusted model exploring the association between contemporary growth and SAHARAN Toolbox outcomes, the covariates were: child years/months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. The derivation of adjusted models using different DAG's was repeated in other analyses described in subsequent chapters.

A chord diagram using standardised scores was constructed using Datagraph (Datagraph) to summarise the associations. A chord diagram displays inter-relationships between variables which are placed as nodes radially around a circle. The chord diagram represents the associations between the variables as arcs that connect these nodes. For this thesis, the width of the line in the chord diagram was in proportion to the size of the association. For clarity in the chord diagram, associations that were not significant across all models were not plotted on the chord diagram. As an exploratory analysis, associations of growth by school-age with all SAHARAN functional outcomes were examined, with general trends illustrated by separate chord diagrams for cognitive and physical function. Detailed tables of associations are also presented in the appendix.

4.2.1.2 Principal components analyses

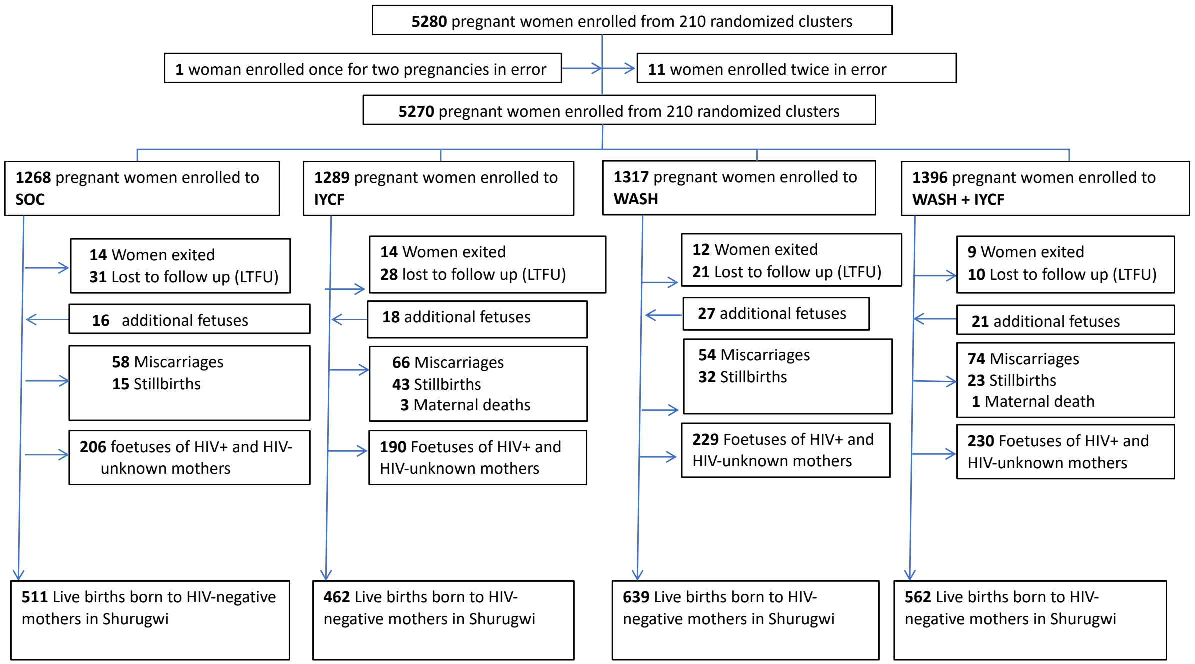
Principal components analyses were performed to reduce the SAHARAN toolbox outcomes into a smaller number of aggregated components. The eigenvalues for these components were observed on a Scree plot and confirmed by parallel analysis to identify the number of components. The components were then derived for each child, and the loading of each component interpreted, then hierarchical clustering was used to group children according to their school-age outcomes. These clusters were plotted using the principal components, and differences between clusters were compared. To explore underlying reasons for these outcomes, contemporary exposures were compared between the hierarchical clusters. These were measured in the caregiver questionnaire and separated into environmental, schooling, caregiver and nurturing factors. Early-life growth and baseline environmental variables were also compared within hierarchical clusters.

4.2.1.3 Contemporary exposures

To examine the impact of contemporary exposures, univariable analysis first explored associations between school-age growth, cognitive and physical function and individual contemporary exposures. To reduce multiple comparisons, the key components from the PCA of outcomes were used combined with the least absolute shrinkage and selection operator (LASSO) on generalised estimating equations (GEE). LASSO-GEE is a machine learning technique that enables variables which do not contribute to the principal components to be identified and discarded. Hence LASSO-GEE was used to identify the contemporary exposures that were irrelevant for the principal components. The remaining contemporary environmental exposures for each PCA component were then discussed.

4.3 Results

Enrolment into SHINE Follow-up: CONSORT diagram



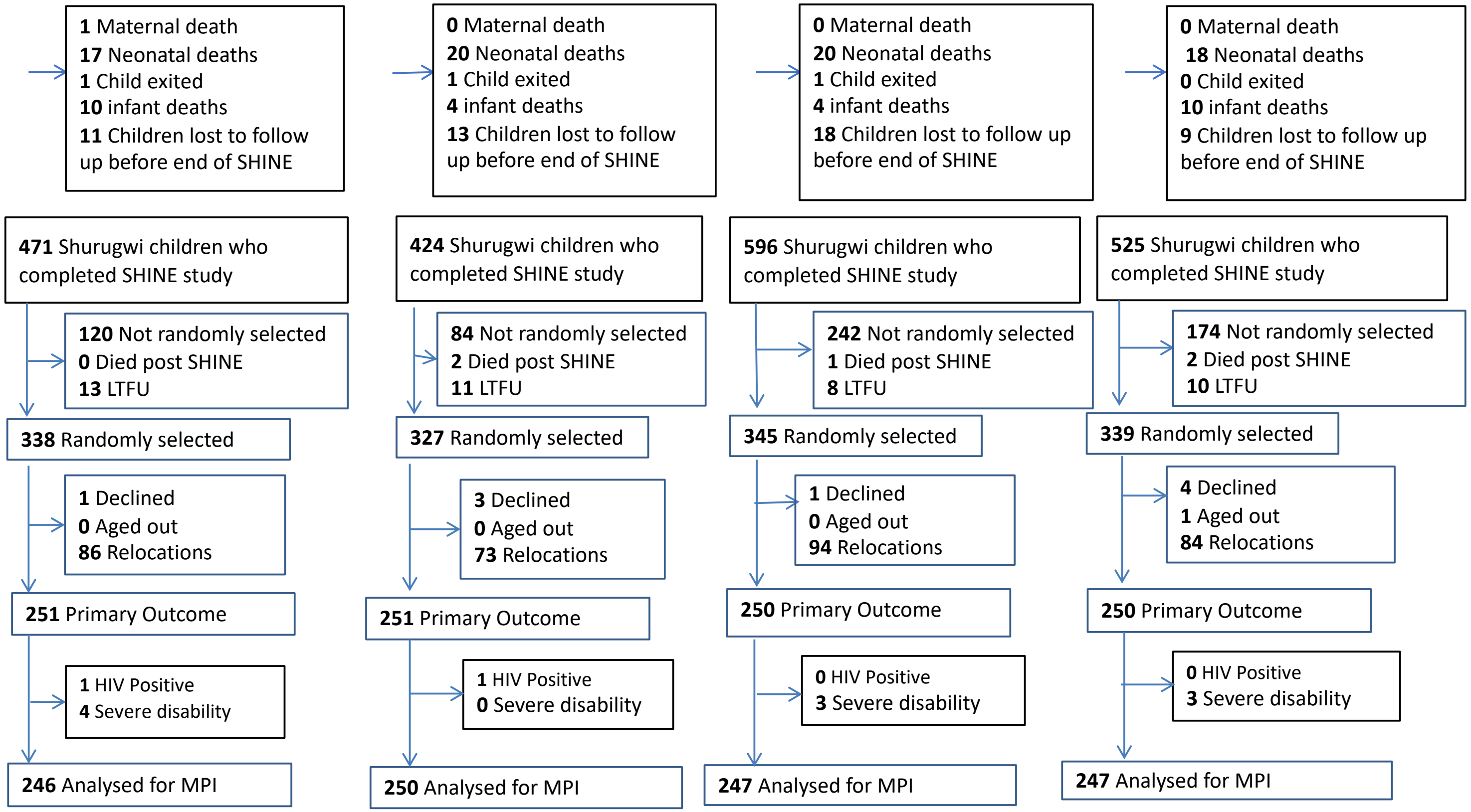


Figure 4-1 CONSORT diagram of children recruited into SFU

The enrolment of children born to HIV negative mothers (CHU) into the SHINE follow-up (SFU) study is summarised in the CONSORT diagram (Figure 4-1). Between 22 November 2012 and 27 March 2015, 5280 pregnant women were enrolled from 211 clusters at median 12 (IQR 9, 16) gestational weeks in Shurugwi and Chirumanzu districts. Of 2174 births from HIV-negative mothers in Shurugwi district only, 3 (0.1%) voluntarily exited the trial, 103 (4.7%) children died, and 51 (2.3%) or moved outside Zimbabwe or were otherwise lost to follow-up; 2017 children in Shurugwi were therefore assessed at the 18-month visit[77]. Five children (0.2%) died and 42 (2.1%) were lost to follow-up after 18 months: they could not be located when they were initially selected for the SFU study. From 1970 available children, 1349 children (68.5%) were randomly selected at age 7 years across all the 4 intervention arms in Shurugwi. Of these, 337 (25%) had relocated out of Shurugwi, 9 (0.7%) declined follow-up, and one child could not be measured before turning 8 years of age due to heavy rains in their location. Overall, 1002 children were assessed at age 7 years; of these, 12 were excluded from the main analysis. For 2 children, this was due to being HIV-positive (the mothers had seroconverted during breastfeeding); the remaining 10 children were excluded due to severe disability (see chapter 3). Therefore, 990 children were analysed for the primary outcome (246 SOC, 250 IYCF, 247 WASH, 247 IYCF+WASH). Poor understanding of the finger tapping test led to 3 further children being removed for this test. For physical function, 1 child was removed from the broad jump and 3 children were removed from the shuttle-run test due to medical reasons (e.g. leg injury, asthma) (see Chapter 3). The WG UNICEF tool assisted with screening but did not provide complete definitions of disability: Some children’s disability status in the clinical notes did not reflect the answers in the WG UNICEF tool. Therefore, both the WG tool and clinical descriptions were used to define disability. Future training should focus on quality control and contemporaneous coding to ensure that any disability is accurately recorded, as well as including acute injury. Given function and disability is a continuum, it would also be helpful in the future to discuss definitions contemporaneously within the fieldwork team.

Cognitive and physical outcomes compared with other cohorts

Among 1002 children in SFU, their mean (SD) age was 7.3 (0.2) years, height-for-age Z-score was -0.5 (0.9), weight-for-age Z-score was -0.6 (0.9) and mean schooling was 3.2 (0.8) years. 51% of SFU were female. Comparisons with other cohorts confirmed the plausibility of the SAHARAN toolbox data. Firstly, cognitive outcomes had plausible values that were comparable to the available literature. For example, the children measured in SHINE had a mean scaled mental processing index (MPI) score of 48 (SD 11) and mean of 3.2 years of schooling (SD 0.8). Subscales also showed normal distributions (see Appendix) with similar scaled raw scores to the rural South African Siyakhula cohort[190]. The School Achievement Test (SAT) had a mean of 46 (SD 28) which was similar to the previously reported value of 41 (SD 21) in a pilot cohort of children in the same setting[192]. Comparisons beyond this are not possible for the SAT, since it was specifically developed for this age range and context. The Plus EF combined total for the three subtests used was 114 (SD 24), although there are no normative data available for PlusEF scores, which reflect executive function. Time for successive finger tapping was 24.0 (SD 6.6) seconds, which was longer than the ~19 (SD 6) seconds observed in stunted children in Jamaica at age 11-12 years, likely due to being slower in completing the task at younger ages[205]. In the SHINE follow-up cohort, children who were almost 8 years were 2 seconds (95% CI 0.2, 3.9) faster than the youngest who had recently turned 7 years. For the Strengths and Difficulties Questionnaire (SDQ) measuring socioemotional function, the mean score in SHINE was 8.6 (SD 5.2), which is remarkably similar to the caregiver-reported scores for UK children aged 5-10 years of 8.6 (SD 5.7)[253]. Other studies have shown increasing scores with further deprivation such as a reported mean of 14.5 (SD 6) in South African orphans[257]. Applying UK-based cut-offs of SDQ score >16 identified 80 children (8%) who were at risk of significant socioemotional problems.

For physical function tests, the values measured in the SHINE cohort also compare credibly to other published data. The mean handgrip strength was 10.7 Kg (SD 1.9), which was similar to a South African cohort with mean 11.2 Kg (SD 4.4) in 8 year old children[254]. The mean broad jump distance was 112.8cm (SD 15.1 cm) which is around the 20th percentile compared to 7-year old European children[255]. This is plausible given that Zimbabwean children had a mean height approximately 10cm shorter[255]. The VO_2max from the shuttle run was 50.7

ml/Kg/min (SD 2.7), which is similar to that for 7-year old children in rural Kenya which measured from 5-18 years[219], although slightly higher than those quoted for HIC settings[258].

The cohort had a mean HAZ of -0.4 (SD 0.8) for girls and -0.6 (SD 0.9) for boys (although absolute heights were similar); WAZ was mean -0.6 (0.8) for girls and -0.7 (0.9) for boys (absolute mean weight was 160g heavier for boys). The overall prevalence of stunting within SHINE at 18 months was 30%[73], and for the SFU cohort was 35.6% for boys and 23.8% for boys (see chapter 5). Proportions of stunting at age 7 years were 2.0% for girls and 6.2% for boys. These results were consistent with boys being more biologically vulnerable to poor linear growth, as has previously been noted[259]. Hence these results suggested considerable catch-up growth, which is explored further in chapter 5. Further comparisons with body composition are dealt with in the next section which examines differences by child sex.

Contemporary characteristics of the cohort

The SHINE follow-up cohort were living within a region of food insecurity and multiple adversities . For example, 294 (30%) of households had experienced one or more deaths in the family since the birth of the child into the SHINE household; 421 (43%) households had experienced a crop failure, of which 240 (24%) had experienced 2 or more crop failures since the birth of the child (Table 4-1)

Adversity for children born to mothers without HIV	**Number of households**
Death in household	30% [294]
2 or more deaths in household	5% [48]
Household member lost paid employment	15% [149]
Household member unemployed >6 months	12% [108]
Household had crop failure	43% [421]
Household had 2 or more crop failures	24% [238]
Household had business failure	32% [308]
Household lost land	3% [30]
Household lost family possessions	16% [159]
Adults in household that are sick or injured, so not able to work for >3 months	10% [100]
Household member with alcohol problem	8% [75]
Household debt causes worry	16% [155]
Have move home 3 or more times since child in SHINE study born	5% [45]

Caregiver was sad or very sad about the last household move	8% [67]
Child in SHINE admitted to hospital overnight	9% [88]
Child in SHINE study had 2 or more hospital admissions	1% [14]
Caregiver separated from child for more than 3 months more than once	8% [79]
Households with no documented adversity	19% [192]

Table 4-1 Adversities experienced within the SHINE cohort by household

A household adversity score was derived by combining adversities of any death, loss of job, crop failure, any loss of land or possessions with the other household adversities listed above (sadness over last move, business failure, household members sick or injured, alcohol or debt problems). This was included as a covariate in later adjusted analyses. Adversities were spread between households, with only 19% having no adversity (see Appendix table A4-2)

Impact of child sex on growth and outcomes

The impact of child sex on SAHARAN toolbox outcomes was examined (table 4-1) because sex may be an important influence on outcomes. A similar table was also constructed to compare contemporary environmental variables by child sex (Appendix table A4-1). The distribution of adversity was also similar between sexes (Appendix figure 4-2).

Outcome	Girls		Boys		GEE Mean difference male compared to female (95% CI)		
	Female N	Mean (SD)	Male N	Mean (SD)	Unadjusted	Model 1 (arm)	Model 2
Mental Processing Index	**506**	**49 (11)**	**484**	**47 (11)**	**-2 (-3, 0)**	**-2 (-3, 0)**	**-2 (-3, 0)**
School Achievement Test	**506**	**50 (29)**	**484**	**41 (26)**	**-9 (-12, -6)**	**-9 (-12, -6)**	**-9 (-12, -5)**
Plus EF Total	**499**	**115 (25)**	**479**	**114 (24)**	**-1 (-5, 2)**	**-2 (-5, 2)**	**-2 (-5, 1)**
Fine motor, sec	**505**	**23 (5.8)**	**481**	**25.2 (7.2)**	**2.3 (1.4, 3.2)**	**2.2 (1.3, 3.1)**	**2.3 (1.4, 3.2)**
Strength & Difficulties questionnaire	**505**	**8 (5)**	**484**	**9 (5)**	**1 (0, 1)**	**1 (0, 1)**	**1 (0, 1)**
Child socioemotional score	500	4 (1)	473	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Grip strength, Kg	**506**	**10.4 (1.9)**	**484**	**11 (1.9)**	**0.6 (0.4, 0.9)**	**0.6 (0.4, 0.9)**	**0.7 (0.4, 0.9)**
Maximum broad jump, cm	505	112.1 (14.9)	482	113.4 (15.4)	1.3 (-0.5, 3)	1.3 (-0.5, 3)	1.5 (-0.2, 3.3)
VO_2max, ml kg^{-1} min^{-1}	**504**	**50.7 (2.6)**	**482**	**51.1 (2.8)**	**0.3 (0, 0.7)**	**0.3 (0, 0.7)**	**0.3 (0, 0.6)**
Diastolic Blood pressure, mm Hg	506	62.3 (7.3)	482	62.4 (7.8)	0.1 (-0.9, 1.1)	0 (-1, 1)	0.1 (-0.8, 1)
Systolic Blood Pressure, mm Hg	506	96.8 (9.4)	482	97.3 (9.2)	0.5 (-0.7, 1.7)	0.5 (-0.7, 1.7)	0.4 (-0.7, 1.6)
Height-for-age Z-score	**506**	**-0.4 (0.8)**	**484**	**-0.6 (0.9)**	**-0.2 (-0.3, -0.1)**	**-0.2 (-0.3, -0.1)**	**-0.2 (-0.3, -0.1)**
Weight-for-age Z-score	505	-0.6 (0.8)	483	-0.7 (0.9)	-0.1 (-0.3, 0)	-0.1 (-0.3, 0)	-0.1 (-0.3, 0)
BMI-for-age Z-score	505	-0.5 (0.8)	483	-0.5 (0.8)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0.1)
Knee-heel length, cm	506	37.5 (1.9)	483	37.3 (1.9)	-0.2 (-0.4, 0.1)	-0.2 (-0.4, 0.1)	-0.1 (-0.4, 0.1)
Head circumference, cm	**506**	**50.8 (1.3)**	**484**	**51.8 (1.4)**	**0.9 (0.8, 1.1)**	**0.9 (0.8, 1.1)**	**0.9 (0.8, 1.1)**
Mid-upper arm circumference, cm	**506**	**17.1 (1.4)**	**483**	**16.8 (1.1)**	**-0.3 (-0.5, -0.1)**	**-0.3 (-0.5, -0.1)**	**-0.3 (-0.4, -0.1)**
Waist circumference, cm	**506**	**53.8 (3.3)**	**483**	**54.3 (2.9)**	**0.5 (0.1, 0.9)**	**0.5 (0.1, 0.9)**	**0.5 (0.1, 0.9)**
Hip circumference, cm	**506**	**61.3 (4.3)**	**484**	**60.4 (3.5)**	**-0.9 (-1.4, -0.4)**	**-0.9 (-1.4, -0.4)**	**-0.8 (-1.3, -0.4)**
Calf circumference, cm	**506**	**23.6 (1.8)**	**483**	**23.3 (1.6)**	**-0.3 (-0.5, -0.1)**	**-0.3 (-0.5, -0.1)**	**-0.3 (-0.5, -0.1)**
Lean Mass index, $Ohms^{-1}$	**501**	**11.8 (1.3)**	**481**	**12.4 (1.3)**	**0.6 (0.4, 0.8)**	**0.6 (0.5, 0.8)**	**0.6 (0.5, 0.8)**
Impedance Index, m^2 $Ohms^{-1}$	**501**	**1.7 (0.3)**	**481**	**1.8 (0.3)**	**0.1 (0, 0.1)**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**
Phase angle, degrees	501	4.9 (0.6)	481	5.0 (0.5)	0.1 (0, 0.1)	0.1 (0, 0.1)	0.1 (0, 0.2)
Total Skinfold thickness, mm	**503**	**28.8 (6.6)**	**484**	**25.3 (5.2)**	**-3.6 (-4.3, -2.8)**	**-3.6 (-4.3, -2.8)**	**-3.6 (-4.4, -2.8)**
Peripheral Skinfold thickness, mm	**504**	**17.2 (3.8)**	**484**	**15.1 (3.3)**	**-2.1 (-2.5, -1.6)**	**-2.1 (-2.5, -1.6)**	**-2.1 (-2.5, -1.6)**
Central Skinfold thickness, mm	**505**	**11.7 (3.5)**	**484**	**10.1 (2.3)**	**-1.6 (-2.0, -1.2)**	**-1.6 (-2, -1.2)**	**-1.6 (-2, -1.2)**
Haemoglobin	506	12.7 (1.2)	484	12.7 (1.2)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.0 (-0.1, 0.2)

Table 4-2 Comparison of SAHARAN toolbox outcomes by child sex.

PlusEF: Executive function tablet based tool, VO_2max: aerobic capacity

4.3.1.1 *Differences in cognitive function by child sex*

Plausible differences by child sex were observed. Firstly, girls appeared to have better cognitive function with higher scores in cognitive processing as represented by the Mental Processing index (+2 marks, 95%CI 0, 3), literacy and numeracy in the school achievement test (+9 marks, 95%CI 6, 12) and executive function from the Plus-EF test (+1 mark, 95%CI -2, 5). Girls had faster fine motor function with an average 2 seconds (95%CI 1, 3) faster to perform the finger tapping task, averaged across both hands. Girls had higher socioemotional function than boys by 1 mark (95% CI, 0, 1). All of these observed effects remained across adjusted models, suggesting the trial arm or factors such as age of the child did not explain the differences observed. There were no significant differences when examining contemporary environmental factors split by child sex, including the total amount of schooling (See appendix Table A4-1) or adversity (Table A4-2).

4.3.1.2 *Differences in physical function by child sex*

Boys had significantly stronger handgrip strength by 0.6 Kg (95%CI 0.4, 0.9), which is well documented in the literature[254,260], and this difference accelerates during puberty due to the influence of testosterone[260]. Boys also had a higher mean broad jump (113.4 cm, SD 15.4) compared to girls (112.1, SD 14.9) though there was only a weak evidence of difference. Mid-upper arm circumference (MUAC), weight and height have also been associated with stronger grip strength in prior studies[260]. However in this cohort, girls had higher MUAC, and boys a lower height-for-age Z-score. The sexes had similar body mass index, so it is useful to examine growth and body composition in more detail.

4.3.1.3 *Differences in Body composition by child sex*

Beyond height, differences in body composition help to explain the differences in physical function observed. Boys had greater impedance index (a measure of lean mass) as well as lean mass index, both of which have been associated with improved physical function such as handgrip strength[261]. Boys had on average 0.6 $Ohms^{-1}$ (95%CI 0.4, 0.8) higher lean mass index (LMI), which is important since LMI removes the contribution of height to lean mass. Boys also had a slight trend towards a greater VO_2max, corresponding to running on average an additional 20 metres on the shuttle run test. This has been previously observed[258] and may also reflect greater lean and less fat mass.

Girls had significantly increased peripheral and central skinfold thicknesses, as has been observed both in Turkey[262] and rural South Africa (Amusa et al.). This would contribute to the observed increased MUAC, hip and calf circumference seen in girls. Skinfold thickness has been shown not to contribute to handgrip strength[263] and also reduces VO_2max by the shuttle run test for children aged 8-16 years[264]. Boys had a larger head circumference than girls, as would be expected from routine growth WHO growth charts up to 5 years[265]. Boys also had a higher waist circumference and girls a higher hip circumference, both of which have been previously observed in similar-aged European children[266,267]. There were no observable differences in contemporary environmental, caregiver or nurturing covariates (See appendix table A).

Overall, clear sex-specific trends in growth and function were observed, with girls having better cognitive and reduced physical function compared to boys. Boys had more lean mass and higher head and waist circumference, whilst girls had higher skinfold thicknesses, hip, MUAC and calf circumferences. All of these trends in growth and physical function had been previously observed in other similar-aged cohorts. The next step was to examine the internal consistency of the different tests within each domain.

Correlation analyses exploring internal consistency

4.3.1.4 *Cognitive function*

Spearman correlation analyses were performed to explore internal consistency within the domains of cognitive and physical function and identify collinear outcomes which would be removed for the principal components analyses. For cognitive function, Spearman correlation matrices for the 5 main cognitive outcomes showed some correlations but all remained below 0.7 (n=956)[268]. Therefore, all cognition variables were chosen as outcomes to contribute to a principal components analysis.

	MPI	SAT	PlusEF	Fine motor	SDQ	Child Socem
MPI	1.00					
SAT	0.64	1.00				
Plus EF	0.49	0.45	1.00			
Fine motor	-0.47	-0.51	-0.46	1.00		
SDQ	-0.13	-0.17	-0.08	0.12	1.00	
Child Socem	0.13	0.13	0.06	-0.10	0.03	1.00

Table 4-3 Spearman correlation between tests of cognitive function in the SAHARAN toolbox.

MPI: Mental processing index, SAT: School achievement test, SDQ: Strengths and difficulties questionnaire, Child Socem: Child socioemotional scale

The strongest correlation was between the Kaufman Assessment Battery for Children (KABC-II) total (represented by the Mental Processing index (MPI)) and the School achievement test (SAT) of 0.64. This was interesting to note since the MPI removes specific knowledge components from the KABC-II to focus on novel puzzles not previously seen in schools[198]. However, in a rural Zimbabwean context, schooling exposure is likely to provide an important source of stimulation and may reflect multiple socioeconomic factors including improved food security from school meals. Academic function is an important marker of cognitive function[269]. One study in the USA compared the KABC-II with the Kaufman Test of Educational Achievement (KTEA), which assesses literacy and numeracy[269]. This showed that the Fluid Crystallised Index (which includes adding specific knowledge subtests within the KABC-II to augment the MPI) had the closest correlation with the KTEA total, whilst the MPI alone over-estimated measured achievement for Hispanic and African-American groups (hence missing markers of worse academic function, potentially due to deprivation and marginalisation). Although used in a different context, this suggests that the school achievement test adds important information on literacy[160], numeracy[163] and academic function[158,160]. The correlation also suggests the possibility of constructing shorter cognitive metrics based on academic function, which may capture some of the variability within the more detailed KABC-II.

As expected, there was moderate correlation between the Plus EF as a measure of executive function[96], and other aspects of cognitive function, including the MPI, SAT[165] and fine motor function[270]. Similarly, for fine motor function, a negative correlation with other cognitive outcomes was expected, representing a shorter time to complete the finger tapping task. Fine motor function has previously been moderately correlated with academic ability[175] and also executive function[270]. There was low correlation of all measures of cognitive function with the child's socioemotional function when measured by the Strengths and Difficulties Questionnaire (SDQ). The negative correlation is plausible given that increased SDQ scores represent greater socioemotional dysfunction. There could be several reasons for the low correlation. Firstly, socioemotional function is a very different cognitive domain compared to others that were directly measured. Secondly, this was a tool administered to the caregiver: the caregiver's opinions potentially add another layer of complexity as the child's function was not directly observed. Finally, although this had been previously piloted[192], verifying the cultural equivalence of behavioural concepts may require further research. The child's socioemotional function also had low correlation with other cognitive domains, but this was not surprising since this questionnaire only asked simple binary questions to the child regarding their own happiness and support in the home[192]. Overall, this correlation analyses suggested all tests of cognitive function should be included in subsequent analyses, including principal component analyses.

4.3.1.5 Physical function

Correlation analyses for physical function showed low correlation between all measurements. The highest correlation observed of 0.36 was between grip strength and broad jump, which was plausible given they measured leg strength and hand strength, respectively.

	Grip strength	Broad jump	VO2max	Systolic BP	Diastolic BP
Grip strength	1.00				
Broad jump	0.36	1.00			
VO_2max	0.15	0.22	1.00		
Systolic BP	0.14	0.08	-0.05	1.00	
Diastolic BP	0.13	0.08	-0.06	0.60	1.00

Table 4-4 Spearman correlation matrix between tests of physical function in the SAHARAN toolbox.

VO_2max:maximal aerobic capacity as measured by level achieved in the shuttle run test. BP: blood pressure

The next highest correlation of 0.22 between broad jump and VO_2max is also plausible given they represent leg strength and level reached in the shuttle run test, respectively. There was low correlation between resting blood pressure and all measures of physical function. This may partly be due to an observed tendency to round blood pressure measurements to the nearest 10mm Hg amongst data collectors. The ALSPAC study showed that height, lean and fat mass was independently and positively associated with blood pressure at 9 years[271]. Other studies have observed increases of blood pressure with body fat[185] and decreases with physical activity[272], in older children of 8-11 years. Overall, this correlation analysis suggested all tests of physical function should be included in subsequent analyses, including principal component analyses.

4.3.4.3 Growth and body composition

As expected, the strength of correlations between different growth measurements varied. Generally, correlation values were higher between measurements that employed similar techniques (eg body circumferences) or elements of fat mass such as skinfold thicknesses and weight. Correlation was poorer when comparing measures of lean (eg lean mass index, phase angle) and fat mass (skinfold thicknesses). Haemoglobin was not correlated with any measurement.

	HAZ	WAZ	BMIZ	Knee heel length	Head circ	MUAC	Waist circ	Hip circ	Calf circ	LMI	Imp Index	Phase angle	Total SFT	Central SFT	Periph-eral SFT	Hb
HAZ	1.00															
WAZ	0.75	1.00														
BMIZ	0.13	0.72	1.00													
Knee-heel length	**0.88**	0.69	0.16	1.00												
Head circ	0.25	0.37	0.31	0.23	1.00											
MUAC	0.38	0.70	0.68	0.40	0.24	1.00										
Waist circ	0.39	0.67	0.63	0.43	0.36	0.50	1.00									
Hip circ	0.56	0.77	0.61	0.56	0.23	0.67	0.55	1.00								
Calf circ	0.52	0.79	0.67	0.53	0.30	0.74	0.58	0.71	1.00							
LMI	0.16	0.44	0.52	0.15	0.26	0.45	0.37	0.34	0.53	1.00						
Imp Index	0.65	0.74	0.46	0.62	0.35	0.56	0.52	0.57	0.69	**0.81**	1.00					
Phase Angle	0.01	0.19	0.32	0.04	0.04	0.28	0.22	0.21	0.25	0.24	0.20	1.00				
Total SFT	0.22	0.46	0.48	0.23	0.04	0.55	0.29	0.53	0.50	0.06	0.16	-0.01	1.00			
Central SFT	0.20	0.42	0.44	0.21	0.02	0.49	0.27	0.46	0.43	0.06	0.15	0.00	**0.88**	1.00		
Peripheral SFT	0.22	0.44	0.44	0.23	0.06	0.53	0.27	0.52	0.48	0.07	0.16	-0.03	**0.94**	0.69	1.00	
Hb	0.03	0.03	0.02	0.04	0.02	0.03	0.02	0.03	0.04	0.03	0.05	0.11	0.03	0.03	0.03	1.00

Table 4-5 Spearman correlation matrix between tests of growth and body composition in the SAHARAN toolbox.

HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMIZ: BMI-for-age Z-score at 7 years, Head circ: Head circumference, MUAC: Mid-upper arm circumference, Waist circ: Waist circumference, Hip circ: Hip circumference, Calf circ: Calf circumference, LMI: Lean mass index, Imp Index: Impedance Index, Total SFT: Total skinfold thickness (from sum of all 4 skinfold thicknesses) Central SFT: Central skinfold thickness (subscapular + suprailiac), Peripheral SFT: PeripheralS skinfold thickness (triceps + calf), Hb: Haemoglobin.

Certain measurements showed a very strong correlation. Knee-heel length and height for age Z-score had a correlation of 0.88, which strongly suggested that tibial growth was in proportion to overall linear growth. In South American cohorts, tibial growth was much shorter in highland children (exposed to greater nutritional stress) than lowland children[273]. For the SHINE cohort, the strong correlation with overall height meant that leg length was not included to reduce collinearity for principal components analysis.

Impedance index and lean mass index had a correlation of 0.81. This was unsurprising since lean mass index, defined as 1/Z (the average impedance), is independent of height[274], whereas 'impedance index' is defined as height-squared divided by average impedance (H^2/Z). Impedance index provides a direct estimate of relative lean mass by including height in the estimation, as lean mass always scales strongly with height[275]. Impedance index is a composite marker of lean mass relative to height. However, since lean mass index and height were also recorded, impedance index was not included in the principal components analysis. Finally, total skinfolds had high correlations of 0.88 and 0.94 with central and peripheral skinfold thickness, respectively, because it is the sum of these two components. However, observing the distribution in skinfold thickness is important because stunted children may accumulate greater central fat[276,277] which may have long-term cardiometabolic risk[278]. Hence total skinfold thickness was removed from principal components analysis due to collinearity.

Overall, there was internal consistency within the domains of cognitive and physical function as well as growth and body composition. Hence the next step was to explore associations of growth and body composition with physical and cognitive function.

Associations of growth by school-age on child function

The effect of child growth and body composition on cognitive and physical function was explored using generalised estimating equations (GEE) that accounted for within-cluster correlation to estimate effect size, with an exchangeable working correlation structure. For the adjusted model, a Directed Acyclic Graph was constructed by considering environmental, maternal and nurturing factors measured in the caregiver questionnaire.

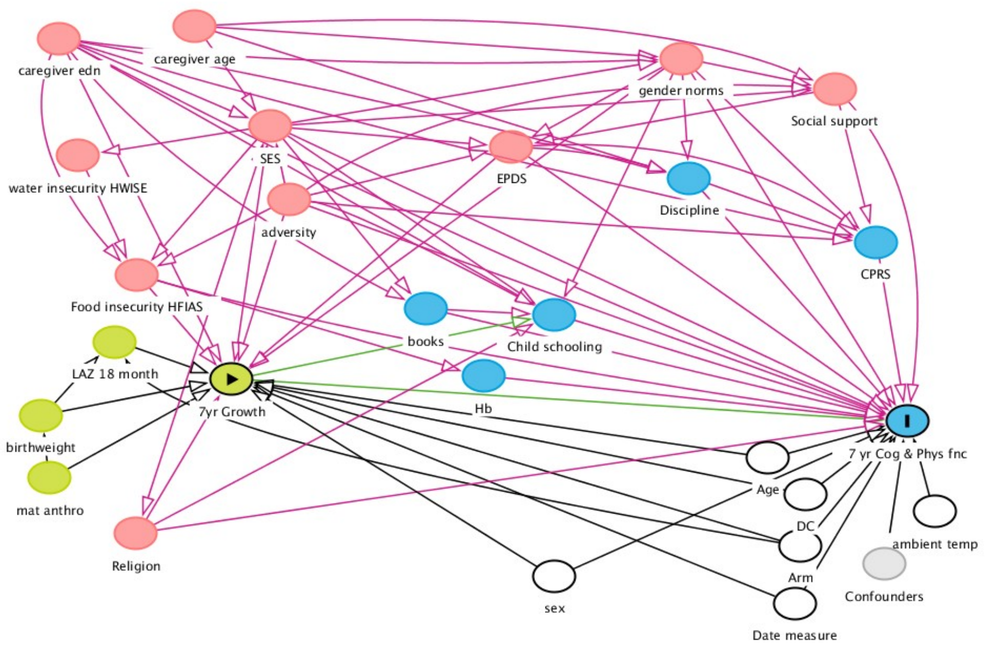


Figure 4-2 DAG for growth by school-age on function

This DAG explored the effect of covariates in the relationship between 7-year growth and cognitive and physical function. Environmental covariates were grouped at the top left, with maternal and nurturing on the right side and trial factors at the bottom right. Caregiver edn: caregiver education, SES: socioeconomic status calculated from wealth index, HWISE: Household water insecurity experiences scale, EPDS: Edinburgh postnatal depression score, Books: number of childrens' books at home, CPRS: Child parent relationship scale, DC: data collector, ambient temp: ambient temperature (from average of start and end temperature of visit), Hb: haemoglobin, mat anthro: maternal height, LAZ 18 month: length-for-age Z-score at 18 months, arm: SHINE intervention arm, 7yr Cog & Phys fnc: 7 year cognitive and physical function, Discipline: caregiver discipline score

This thesis used directed acyclic graphs (DAGs) to identify the confounding variables that were required within adjusted models. Hence the DAG was drawn on Dagitty and the variables for adjustment were identified before examining the data in detail. The adjusted model therefore included the following covariates: age, sex, intervention arm, study nurse, date measured, ambient temperature, total child schooling exposure, caregiver discipline, caregiver depression score (EPDS), food insecurity score (HFIAS), religion, socioeconomic status wealth index score, social support score, adversity score, number of children's books, caregiver years of education, and gender norms score.

Detailed tables for the associations are included in the appendix for growth (Table A4-2 to A4-7) and physical function (Table A4-8 to A4-12). However, key standardised associations for the fully adjusted models were summarised in the chord diagrams (Figure 4-2 and Figure 4-3).

Associations of school-age growth with cognitive function

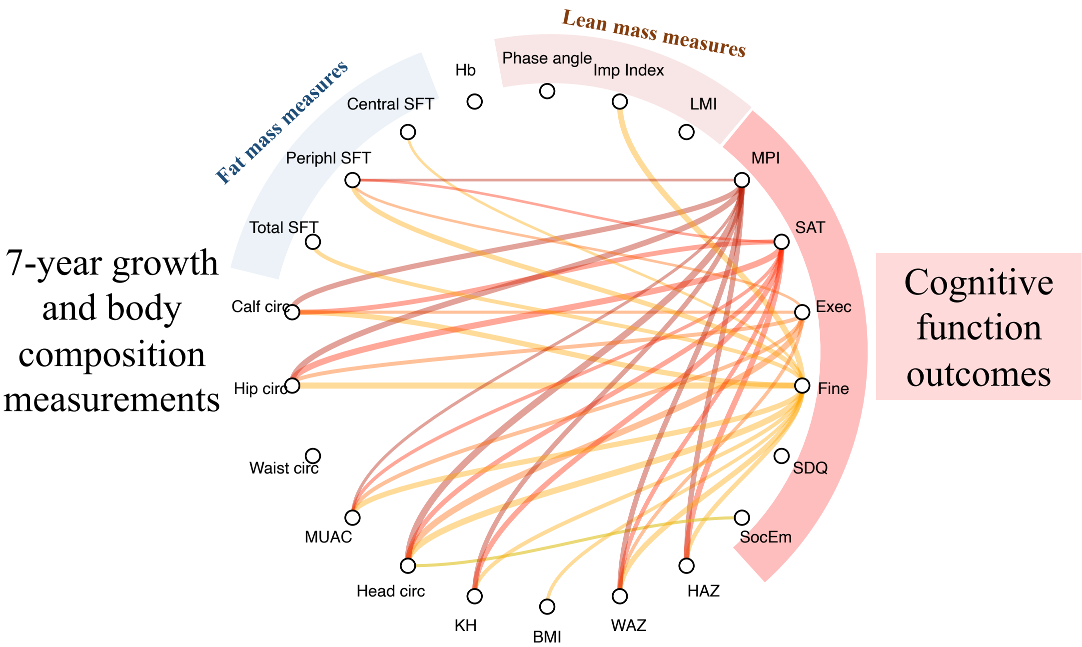


Figure 4-3 Chord diagram exploring contemporary growth associations with cognitive function.

The Chord diagram showed standardised significant associations that remained in adjusted models between 7-year growth measurements and cognitive function outcomes. Mental Processing Index (MPI), School Achievement Test (SAT), PlusEF total measuring executive function (Exec), Fine motor coordination (Fine), SDQ: Strength and Difficulties Questionnaire, Child Socioemotional Function (SocEm). Phase angle, Imp Index: Impdedance Index, LMI: Lean mass index, Hb: Haemoglobin, Central SFT: Central skinfold thickness, Periphl SFT: Peripheral skinfold thickness, Total SFT: Total Skinfold thickness, Calf circ: Calf circumference, Hip circ: Hip circumference, Waist circ: Waist circumference, MUAC: Mid-upper arm circumference, Head circ: Head circumference, KH: knee-heel length, BMI: Body mass index, WAZ: weight—for-age Z-score, HAZ: Height-for-age score. Note that the width of the line is proportional to the size of the association between standardised variables, and is plotted on the same scale for all chord diagrams. Unadjusted associations that did not remain significant in adjusted GEE models were not plotted to improve clarity.

7-year growth and body composition showed associations with cognitive function, particularly with head circumference across all directly measured outcomes. Head circumference mainly reflects early-life growth, particularly up to the first 2 years of life [279]. A wide range of head size is compatible with normal brain function[279] but multiple studies have shown an association between small head circumference and worse neurological outcomes[280-282] or larger head size and better neurological outcomes[283,284]. When adjusting for height, head circumference has been associated with adult occupation[285]. Head circumference has been shown to be the most relevant anthropometric parameter associated with school performance[286]: For example, a remarkably detailed cross-sectional study of 4509 Chilean children was performed, which measured 2000 variables of intellectual, socioeconomic, sociocultural, familial, demographic, and educational factors. By 15 years of age, head circumference for age Z-score was the most useful nutritional indicator associated with scholastic achievement[287].

Mid-upper arm circumference (MUAC) and calf circumferences were also associated with multiple measures of school-age cognitive function (Figure 4-3). MUAC may more accurately reflect current nutritional status than head circumference[288], as it provides a measure of both peripheral fat and lean mass. In one study in Malawi, a school feeding program improved both MUAC and executive function[289]. It is plausible that mid-upper arm and calf circumferences are also identifying improved nutrition, which may reflect both improved lean and peripheral fat mass.

Peripheral skinfold thickness is a more direct measure of peripheral fat and was associated with all measures of cognitive function (Figure 4-3). Early-life long chain fatty acids play an important part in brain development and myelination, which may be reflected by peripheral skinfolds which illustrate earlier fat accretion[290] (see chapter 5). By contrast, central and total skinfold thicknesses were only associated with fine motor function, whilst waist circumference was not associated with any measure of cognitive function. There is some evidence in high-income countries that increasing adiposity is associated with worse cognitive function[291,292]; however, this is complicated by the association of adiposity and lower socioeconomic status in high-income countries[293]. In addition, some evidence suggests that distribution of fat in relation to child weight is important: for example, one study showed that visceral adipose tissue was associated with lower cognitive function in obese children, but provided a benefit in normal weight children[294]. In low-income settings with low prevalence of obesity, greater skinfold thickness may be associated with improved cognitive function[295]. This may also relate to improved nutrition, with potential contributions from increased birthweight, early-life and school-age growth[295]. This is of relevance to the SHINE follow-up cohort, given that only 6/990 children had a BMI Z-score > 2, which could be classified as obese. Of note, birthweight and early-life growth were also associated with peripheral skinfold thickness in the SHINE cohort (see chapter 5). There may also be a contribution of sex (Table 4-2), since girls had both increased skinfold thickness and improved cognitive function, although regression models with sex as an adjustment variable continued to show an association.

Lean mass index, impedance index and phase angle were not generally associated with cognitive function. The exception to this was that impedance index was associated with fine motor function, which supports the strong association of measured lean mass with physical function (Figure 4-3), given that fine motor function incorporates both cognitive and physical function. This could partly be because bioimpedance generally measures the signal from hand to foot so does not measure the brain directly. In general, few studies have explored the impact of school-aged lean mass on child cognitive function. There is some evidence that lean mass in early life is associated with early cognitive function in Ethiopia at 2 years[296], and at 5 years[297]. This is likely to continue throughout life given lean mass associates with improved cognitive function in the elderly[298]. Some evidence links improved exercise with improved cognitive function in obese children[299], but not specifically with improving lean mass, whilst two other randomised trials of an exercise intervention have shown no effect on cognitive performance[300,301]. Two systematic reviews have suggested a possible effect of physical activity on cognitive function but with variable and inconsistent evidence[182,302]. One study in Italy has shown a moderate correlation between cognition and physical function in direct measurement[303]. However, in this study, associations between physical and cognitive function were explored using hierarchical clustering, to reduce the impact of exploring multiple outcomes.

There were no associations between growth measures and socioemotional function as measured by the SDQ. This could be because socioemotional function is a separate cognitive domain or because the SDQ was the only measure relying on caregiver report. Only head circumference was associated with the child's own socioemotional score, which is also plausible, given this score was a simple questionnaire administered to the child on how they felt about their level of support in the home.

HAZ and WAZ were associated with multiple measures of improved cognitive function (Fig 4-3). This is plausible, since WAZ would include peripheral fat mass, and HAZ is correlated strongly with WAZ (0.75), as observed in Table 4-5. However, in general, a recent systematic review showed that interventions that improve HAZ have a small impact on cognition, such that intervention effects on HAZ are not a good proxy measure for cognitive outcomes[76].

Observational cohorts have also shown an impact of growth on cognition. The Young Lives observational cohort of 8062 children in Ethiopia, India, Peru, and Vietnam similarly showed that height-for-age Z-score (HAZ) at 8 years was associated with improved cognitive function, measured by both year in school, numeracy and literacy measures[304]. The Young Lives cohort also showed that catch-up growth improved cognitive function, but overall scores were still below those who had never been stunted[304]. Similar findings, with a benefit of catch-up growth (although not complete catch-up in function) were also reported in Vellore as part of the MAL-ED cohort[305]. Overall for SHINE Follow-up, school-age growth was associated with cognitive function, particularly head circumference and measures of peripheral subcutaneous fat, including skinfold thicknesses and peripheral body circumferences. This provided an interesting insight into the importance of peripheral fat mass in associations with cognitive function in a population with low levels of obesity. The observed associations were small, and therefore not seen in the previous pilot study with its smaller sample size[192]. The next stage was to examine how growth and body composition measures associated with physical function.

Associations of school-age growth with physical function

Generally, 7-year growth and body composition showed stronger associations with physical function than with cognitive function, as observed by the width of the lines in the chord diagram (Fig 4-4).

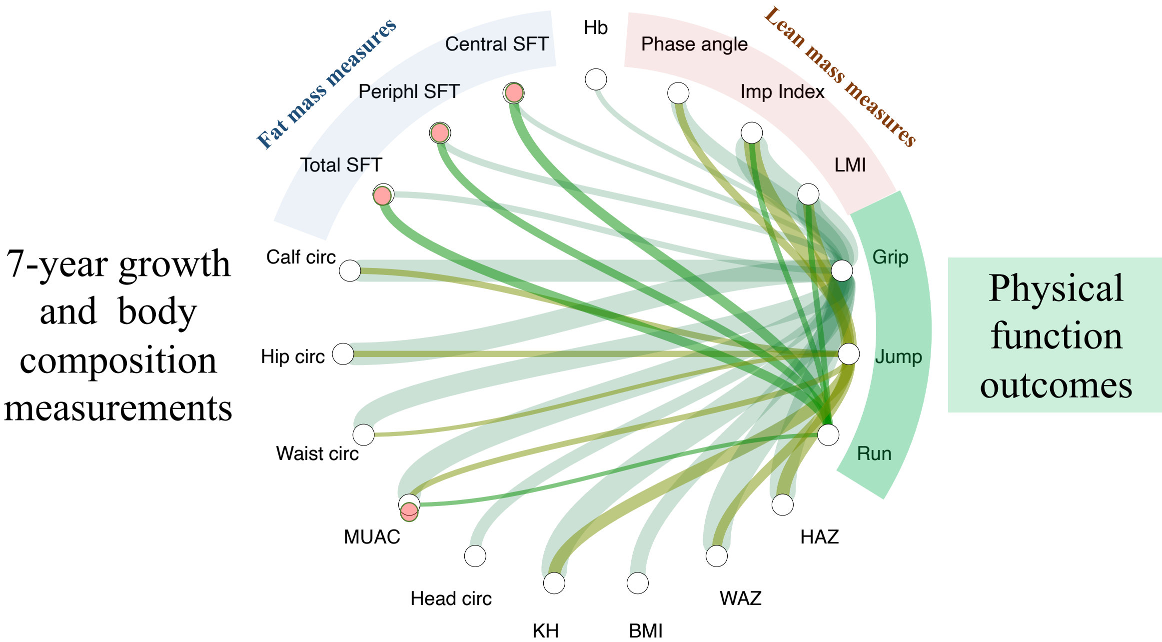


Figure 4-4 Chord diagram exploring contemporary growth with physical function

Chord diagram showing standardised significant associations in adjusted models between 7-year growth measurements and physical function outcomes of grip strength (Grip), broad jump distance (Jump) and VO2max (Run). Phase angle, Imp Index: Impedance Index, LMI: Lean mass index, Hb: Haemoglobin, Central SFT: Central skinfold thickness, Periphl SFT: Peripheral skinfold thickness, Total SFT: Total Skinfold thickness, Calf circ: Calf circumference, Hip circ: Hip circumference, Waist circ: Waist circumference, MUAC: Mid-upper arm circumference, Head circ: Head circumference, KH: knee-heel length, BMI: Body mass index, WAZ: weight—for-age Z-score, HAZ: Height-for-age score. Note that the width of line is proportional to the size of the standardised association (on the same scale as Figure 4-2). Central SFT, Peripheral SFT and Total SFT are highlighted in red as they were negatively associated with VO2max. Note that the width of the line is proportional to the size of the association between standardised variables, and is plotted on the same scale for all chord diagrams.

The magnitude of associations between growth and measures of strength (grip strength and broad jump) were greater than between growth and cardiovascular fitness (the shuttle run test) (Figure 4-4). Grip strength was associated with all measures of growth. However, for grip strength the magnitude of the association (and hence the width of the chord) was noticeably weaker for skinfold thicknesses and head circumference than for measures of lean mass including impedance and lean mass indices. Lean mass is strongly associated with height, where the impedance index $(Height)^2/Z$ provides a composite marker of muscle and organ mass. Therefore it is unsurprising that child height was related to grip strength, and this association has previously been noted at school-age[306]. This was similarly true for other proxy measures of lean mass such as height or weight, or body circumferences which may include a contribution of muscle such as MUAC, calf, hip or waist circumferences. Similarly height was associated with broad jump distance, which is plausible since stature has been associated with the strength of other muscles[307]. There may be a global effect of stature (possibly also mediated by bone growth) on whole-body muscle strength[308]. Height is closely associated with knee-heel length, weight and hence also body mass index.

The shuttle run test measured cardiovascular fitness by recording the level achieved in the shuttle run and then converting that to VO_2max as a measure of aerobic fitness. Of note, there was no association between VO_2max and weight, height, BMI or body circumferences (except MUAC), suggesting insight from more detailed body composition measurements was needed. When components of lean and fat mass were measured individually, increasing lean mass and impedance indices were associated with improved cardiovascular fitness or VO_2max. This is plausible since lean mass has been shown to increase with both strength and fitness training[309]. By contrast, peripheral and central skinfold thicknesses and MUAC were negatively associated with VO_2max (marked in red on Figure 4-4). This is consistent with previous studies which showed increasing adiposity reduces cardiovascular fitness [310], and this is more sensitive than measuring BMI[311]. Research is emerging in children as young as 5 years old that adiposity impedes cardiovascular fitness, as measured by recovery time[312]. Similarly a recent study in South Africa on school-age children performing the PERF-FIT performance battery of tests showed that underweight children were agile (with improved cardiovascular fitness) but lacked power (leg and arm muscle strength)[313]. The negative association with MUAC is likely from the contribution of increased subcutaneous fat to MUAC. Muscular strength has been inversely associated with increasing adiposity in children and adolescents in high-income environments[177]. Therefore the association of lean mass with improved (and fat mass with reduced) cardiovascular fitness does support trends observed globally[103].

Diastolic and systolic blood pressure were positively associated with all measures of growth apart from head circumference. This is physiologically plausible, since blood pressure increases with the size of the child. Hence blood pressure was not included in the physical function chord diagram (Fig 4-4), to aid visualisation for the directly measured tests of fitness and strength. There is some evidence that rapid postnatal weight gain leading to an increase in body mass index (but not height) is associated with increasing blood pressure by school-age[314]. Related to this, blood pressure (BP) can be increased in stunting, particularly in combination with becoming overweight[315]. However, in the SHINE follow-up cohort, no overweight children with WAZ > 2 had a blood pressure over the 90th centile for age [one child was referred to clinic for hypertension >99th centile, but the WAZ in this child was 1.3]. In contrast, BP in 8 year-old children in Nepal was independently negatively associated with leg and kidney length[34]. Although this was not observed in the SHINE cohort at age 7 years, BP remains a useful marker to monitor for later cardio-metabolic risk and hence will be measured repeatedly as the cohort ages[316].

Overall, associations between growth and cognitive function were considerably smaller than associations between growth and physical function. The highest standardised GEE coefficient was 0.15 for the association between head circumference and MPI, compared to a value of 0.63 for the association between impedance index and grip strength. Having compared individual outcomes with previous cohorts, examined effects of child sex, observed internal consistency and explored the associations of growth with function, the next step was to perform a principal components analysis to combine the outcomes into a smaller number of aggregated components.

Principal components analysis of outcomes

A principal components analysis of the multiple SAHARAN outcomes was performed to help visualise overall features within the dataset. This aimed to explore the outcomes by a data reduction step, using a smaller number of aggregated components. A Scree plot of eigenvalues identified 5 components, which together explained 61% of the variance in the dataset (see Appendix figure A4-2). This was confirmed by a parallel analysis. The loadings within the

Principal Component number		PC1	PC2	PC3	PC4	PC5
Principal Component name		Nutritional Status	Cognitive	Physical	BP	HAZ & Phase angle
Standardised SAHARAN Variables	Height-for-age Z-score (HAZ)	0.24	0.04	0.12	-0.12	-0.59
	Weight-for-age Z-score (WAZ)	0.36	-0.05	0.05	-0.11	-0.18
	Body Mass Index Z-score	0.31	-0.12	-0.04	-0.03	0.33
	Head circumference	0.15	0.05	0.19	-0.18	-0.15
	Mid-upper arm circumference	0.33	-0.08	-0.09	-0.02	0.13
	Waist circumference	0.29	-0.12	0.06	-0.06	-0.02
	Hip circumference	0.34	-0.04	-0.11	-0.01	-0.08
	Calf circumference	0.34	-0.06	-0.01	-0.08	0.03
	Lean mass index (LMI)	0.21	-0.07	0.34	-0.01	0.26
	Phase angle	0.11	-0.04	0.25	0.13	0.56
	Peripheral skinfold thickness	0.24	-0.05	-0.42	-0.03	-0.01
	Central skinfold thickness	0.23	-0.11	-0.42	0.06	0.04
	Mental Processing Index	0.08	0.47	-0.12	0.08	0.06
	School achievement test	0.09	0.46	-0.15	0.04	0.03
	PlusEF Executive function	0.08	0.43	-0.06	0.02	0.09
	Fine motor	0.09	0.43	-0.08	-0.02	0.06
	Strength & Difficulties Qu	0.02	0.14	-0.13	0.14	0.04
	Child Socioemotional Scale	0.02	0.13	0.08	-0.07	-0.06
	Grip Strength	0.22	0.08	0.35	-0.03	-0.05
	Broad Jump	0.10	0.25	0.32	0.04	-0.01
	VO2max (Shuttle run)	-0.01	0.15	0.29	-0.14	-0.03
	Systolic Blood Pressure	0.10	-0.07	0.09	0.65	-0.14
	Diastolic Blood Pressure	0.10	-0.01	0.08	0.65	-0.16

Scale
-0.40
-0.3
-0.20
-0.1
0.00
0.1
0.20
0.3
0.40

5 components were plotted as a heat map to help visualise how variables were grouped together (Figure 4-5).

Figure 4-5 Principal components analysis

Principal components analysis showed 5 components which represented 61% of the variability of the dataset. They were general growth, cognition, physical function and lean mass, height and phase angle.

The first component (PC1) mainly loaded around variables for nutritional status, particularly BMI, weight and body circumferences. The second component (PC2) loaded particularly on direct measures of cognitive function. This is interesting to note, as only small associations with growth were noted with cognitive function. The third component (PC3) was mainly focused on physical function and lean mass, although skinfold thickness also negatively loaded in this component. This is also plausible, since lean mass had strong associations with all aspects of physical function (Figure 4-5) whereas fat mass had negative associations with cardiovascular function. The fourth component (PC4) primarily reflected blood pressure, which was associated with all aspects of growth. The final component (PC5) reflected height and phase angle. The next step was to generate principal components scores for each child and then explore if there was any hierarchical clustering of the PCA outcomes which may suggest that children form distinct groups based on growth and function.

Hierarchical clustering of outcomes

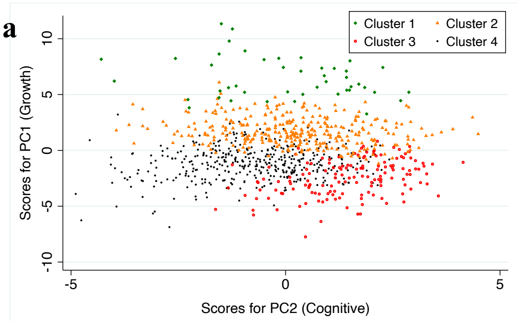
Hierarchical clustering of the standardised outcomes from the SAHARAN toolbox used for PCA was performed, and a dendrogram was plotted (see Appendix, Figure A4-3). Examining the dendrogram suggested that four clusters were appropriate, which also aided distributions to be visualised by quadrant. The distribution of children was skewed towards two larger clusters (clusters 2 and 4, Table 4-6), but the smaller groups had more females. Age was similar between clusters. Distribution by arm was also similar (see Appendix table A4-13).

Hierarchical Cluster number	% [number in each cluster]	% [female]	Mean age of child / years (SD)
1	4.9% [46]	69.6% [32]	7.4 (0.3)
2	35.8% [339]	51.6% [175]	7.3 (0.2)
3	15.9% [151]	61.6% [93]	7.3 (0.3)
4	43.4% [411]	44.5% [183]	7.2 (0.2)
total	100.0% [947]	51.0% [483]	7.3 (0.2)

Table 4-6 Distribution of children into hierarchical clusters

A series of graphs were drawn to plot different combinations of principal components to see if children's function clustered within these groups. By plotting PC1 (nutritional status) against PC2 (cognitive and lean mass) (Figure 4-6), it could be seen that cluster 1 had the best nutritional status and also relatively good cognitive and physical function. Cluster 3 has the lowest values for nutritional status represented by PC1 but relatively high cognitive scores (Figure 4-6a). This may suggest potential 'sparing' for cluster 3 where the brain has been prioritised. Cluster 2 had moderate cognitive function and cluster 4 had poor cognitive function.

a



b

Individual test score per hierarchical cluster

Cluster	n	Mean MPI (SD)	Mean SAT (SD)	Mean PlusEF (SD)	Mean Fine motor (SD)
1	46	54 (12)	68 (28)	129 (21)	21 (4)
2	339	51 (11)	53 (27)	121 (21)	22 (5)
3	151	54 (10)	67 (25)	126 (22)	22 (5)
4	411	43 (9)	30 (18)	104 (23)	27 (8)
Overall	947	48 (11)	46 (28)	115 (24)	24 (6)

c

Growth measures per hierarchical cluster

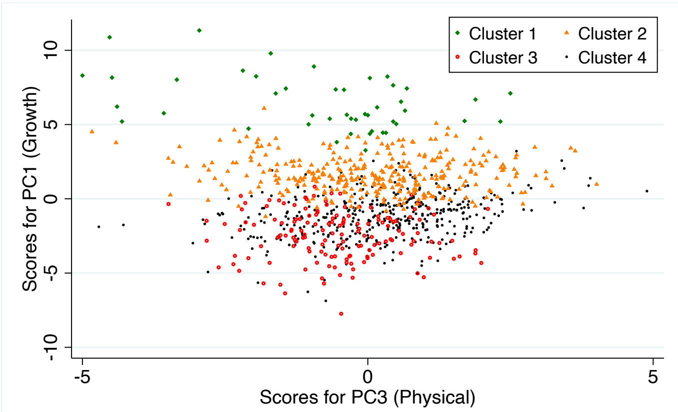
Cluster	n	Mean HAZ (SD)	Mean WAZ (SD)	Mean BMI (SD)	Mean Head circ (SD)	Mean MUAC (SD)	Mean Waist circ (SD)	Mean Hip circ (SD)	Mean Calf circ (SD)	Mean LMI (SD)	Mean Phase angle (SD)	Mean Peripheral SFT (SD)	Mean Central SFT (SD)
1	46	0.6 (0.8)	1 (0.6)	0.9 (0.6)	51.9 (1.3)	19.9 (1.1)	60.1 (2.9)	69.4 (3.8)	26.8 (1.2)	13.6 (1.2)	5.3 (0.5)	23.6 (4.1)	16.8 (5.1)
2	339	-0.1 (0.7)	-0.1 (0.5)	-0.1 (0.6)	51.8 (1.3)	17.5 (0.8)	55.4 (2.3)	62.9 (2.7)	24.4 (1.1)	12.6 (1.1)	5 (0.6)	17.4 (3.4)	11.6 (2.6)
3	151	-1 (0.8)	-1.5 (0.7)	-1.4 (0.7)	50.7 (1.3)	15.9 (0.8)	51.2 (2.3)	57.7 (2.5)	21.9 (1.1)	11.1 (1)	4.8 (0.5)	14.4 (2.7)	9.6 (1.8)
4	411	-0.8 (0.8)	-1 (0.6)	-0.7 (0.6)	51 (1.4)	16.4 (0.8)	53.3 (2.3)	59.3 (2.3)	22.8 (1.2)	11.9 (1.2)	4.9 (0.5)	14.9 (2.7)	10.1 (2.1)
Overall	947	-0.5 (0.9)	-0.7 (0.8)	-0.5 (0.8)	51.3 (1.4)	16.9 (1.2)	54 (3.1)	60.9 (3.8)	23.4 (1.6)	12.1 (1.3)	4.9 (0.5)	16.1 (3.7)	10.9 (2.9)

Figure 4-6 Hierarchical clustering of nutritional status against cognitive function

Hierarchical clustering of SAHARAN outcomes identified 4 clusters. a) : Graph showing principal component 1 (which loaded mainly on nutritional status) against principal component 2 (which loaded mainly on cognitive measures). This showed cluster 3 had relatively poor growth but preserved cognitive function. b) Mean cognitive values of each cluster corroborating cluster 3 has relatively spared cognitive function. c) Nutritional status measures by cluster (representing PC1) shows that cluster 1 has the highest nutritional status, and cluster 3 has lowest nutritional status in all measures.

This potential ‘sparing’ mechanism within cluster 3 for cognition was not present when PC1 was plotted against PC2, which represented physical function (Figure 4-7). Similarly, no sparing mechanism for cluster 3 was observed when PC1 was plotted against the other principal components PC4 and PC5.

a



b

Physical function test score and body composition per hierarchical cluster

Cluster	n	Mean Grip strength (SD)	Mean Broad jump (SD)	Mean VO2max (SD)	Mean LMI (SD)	Mean Phase angle (SD)	Mean Peripheral SFT (SD)	Mean Central SFT (SD)
1	46	13.7 (2.2)	121.2 (16.5)	50 (2.8)	13.6 (1.2)	5.3 (0.5)	23.6 (4.1)	16.8 (5.1)
2	339	11.3 (1.7)	115.9 (14.9)	51 (2.8)	12.6 (1.1)	5 (0.6)	17.4 (3.4)	11.6 (2.6)
3	151	9.7 (1.4)	112.6 (12.5)	50.8 (2.5)	11.1 (1)	4.8 (0.5)	14.4 (2.7)	9.6 (1.8)
4	411	10.2 (1.8)	109.7 (15.2)	51 (2.7)	11.9 (1.2)	4.9 (0.5)	14.9 (2.7)	10.1 (2.1)
Overall	947	10.7 (1.9)	112.9 (15.1)	50.9 (2.7)	12.1 (1.3)	4.9 (0.5)	16.1 (3.7)	10.9 (2.9)

Figure 4-7 Hierarchical clustering of nutritional status against physical function

Graph showing principal component 1 (nutritional status) plotted against principal component 3 (featuring physical function and body composition measures). Cluster 3 had poor physical function on all 3 measures and also reduced lean and fat mass measures compared to the other clusters. Cluster 4 had the lowest broad jump but slightly higher VO_2max and grip strength than cluster 3, with higher lean mass index and skinfold thicknesses.

Cluster 2 had the second-best level of physical function, while cluster 4 had reasonable handgrip strength and VO_2max scores but a low broad jump distance. Cluster 3 had lowest values for all the other principal components PC3, PC4 and PC5, (Appendix Fig A4-4).

Having observed that cluster 3 was performing better on cognition, despite poor growth and physical function, comparisons between hierarchical clusters and contemporary covariates measured in the caregiver questionnaire were made (see Appendix). Of note, cluster 1 generally had better socioeconomic status, food security, caregiver education, lower caregiver depression and higher scores on parent-child relationship. Cluster 3 had slightly higher levels of caregiver schooling (10.2 years compared to an average of 10.0 years) and lower caregiver depression score (EPDS 2.8 compared to average score of 3.4) than cluster 2 and 4, but other environmental, maternal and nurturing factors were similar. Hence it is plausible some of the improved cognitive function of children in cluster 3 was from the benefit of improved caregiver schooling and caregiver mental health compared to clusters 2 and 4.

Early-life growth and baseline factors were also examined (although this is explored in more detail in chapter 5). Cluster 3 had the lowest birthweight and markers of growth in the first 18 months, suggesting early-life growth was not contributing to the improved cognitive function seen at 7 years. Early-life environmental factors were also explored: cluster 3 had moderately increased baseline socioeconomic status (0.5 compared to 0.2 average) and maternal schooling (mean 10.1 compared to 9.7 years), but other baseline factors were similar. The increased years of maternal schooling was consistent with the slight increase in caregiver schooling recorded 7 years later. Age of child was similar, but both clusters 1 and 3 had a higher proportion of girls (61.6% compared to an average of 51.0%). It is plausible that the well-preserved cognitive function in cluster 3 was predominantly due to a combination of higher proportion of girls, with slightly improved caregiver education and lower caregiver depression. Girls had better cognitive function and reduced physical function (Table 4-2) which fits with the characteristics of cluster 3. It is also plausible that other unmeasured confounders may have contributed to the relative resilience of cluster 3.

Overall, cluster 1 had the highest values, representing optimal growth and function, with a higher proportion of females, but was a small group (N=46). Cluster 2 had 339 children, with good physical function and growth, but relatively poor cognitive function. Cluster 3 had good cognitive function but poor growth and physical function, reflecting impaired early childhood growth, but with a higher proportion of females, and slightly higher caregiver education. Cluster 4 had 411 children, and came 3rd in physical function but last in cognitive function. Cluster 4 also had poor early-life growth, but contemporary factors were fairly similar across all hierarchical clusters. Having observed how the cohort function was associated with growth, and how principal components analysis enabled hierarchical clustering to group children based on growth and function, the final stage was to examine the impact of contemporary covariates on the principal components.

LASSO GEE of contemporary exposures

To reduce multiple comparisons, each of the five principal components had a 10-fold cross validation with the least absolute shrinkage and selection operator (LASSO) using generalised estimating equations (GEE). This was performed to find the lambda tuning parameter. When lambda is small, then the result is essentially based on least squares estimates. As lambda increases, shrinkage (ie the loss function within LASSO) occurs so that variables remaining near zero can be identified and discarded. Therefore, this value of lambda on the LASSO GEE enables variables to be identified that were not contributing to the principal components analysis. Once the value of lambda was found, a LASSO GEE identified which standardised contemporary variables were still associated with each PCA component.

	Principal component number	PC1	PC2	PC3	PC4	PC5
	Description of principal component	Nutritional status	Cognitive	Physical & lean mass	Blood pressure	HAZ, Phase angle
	Lambda	1.17	0.53	0.52	0.50	2.51
Study	Intervention arm				X	X
	Calendar date measured					
	Data collector					
	Ambient temperature					
Child	Sex					X
	Child age, yr			X		X
	Child schooling			X	X	X
Environment	Household (HH) religion	X				X
	HH Socioeconomic scale	X		X		X
	HH food insecurity (HFIAS)	X		X	X	X
	HH diet diversity (HDDS)	X	X	X	X	X
	HH Adversity score	X		X	X	X
	Female-headed household	X			X	X
	HH number of children		X	X	X	X
	HH number of adults	X			X	X
	Children's books at home	X		X		X
Nurture / Caregiver	Caregiver schooling years	X		X	X	X
	Caregiver Depression (EPDS)	X				X
	Caregiver gender norms		X	X	X	X
	Caregiver Social support	X		X	X	X
	Caregiver child relationship	X			X	X
	Discipline score	X		X	X	X

Table 4-7: Results from the LASSO-GEE for contemporary factors

Results from the least absolute shrinkage and selection operator (LASSO-GEE) application to the GEE, showing which contemporary variables remain after the lambda value is applied to each principal component. X means the variable no longer remains, so is not associated with the principal component outcome. HFIAS: Household food insecurity assessment scale, HDDS: household diet diversity score, EPDS: Edinburgh Postnatal Depression score

All variables contributed to at least one of the principal components. Examining the remaining variables, the trial variables generally remained. Intervention arm may have multiple associations (see Chapter 7), as does the date of measurement, which affects food security and multiple socioeconomic indicators. The study nurse / data collector conducting the assessment is likely also to have an impact on all outcomes measured. For child outcomes, child sex would be expected to influence all components; it did not remain for PC5, but variables such as HAZ and BMI also contributed to PC1 and PC3. Child age would also contribute to growth and cognition, although not for PC3 and PC5 which is surprising, but may be included in PC1. Child schooling is plausibly associated with PC2, which predominantly reflects cognition[317] and may also influence PC1 (nutritional status) due to school feeding programs or as a measure of household socioeconomic status and wellbeing which affect growth.

For environmental factors, it is logical that household socioeconomic scale, food insecurity and adversity affect cognition, as represented by PC2. It is well documented that socioeconomic status is a risk factor for poor cognitive development in children[318,319]. Similarly, adversity including food insecurity has well-known effects on child development and lifelong health[85]. A female-headed household may be viewed as a marker of adversity in Zimbabwe, with reduced food security[320], hence it could affect child cognitive and physical function[321]. Number of children in the household may plausibly affect PC1 due to reduced nutritional status in settings where there are more children. Similarly the number of adults in a household may improve their socioeconomic position if there is more subsistence farming or employment, but may also increase poverty due to higher food requirements, as has been reported in peri-urban settings[322]. Finally for household factors, the number of children's books at home were associated with child cognition, which was plausible, and hence why it is included in the UNICEF Multi-indicator cluster surveys (MICS)[231].

For caregiver factors, caregiver education has been associated with cognitive function in a similar cohort in South Africa[317]. Similarly caregiver depression is recognised as a risk factor for child cognitive development[318]. It may also potentially affect a child's motivation, hence affecting PC2, although it is difficult to understand how it would affect blood pressure without affecting nutritional status (PC1). Caregiver gender norms may also affect growth and function, as has previously been shown in early life within the SHINE cohort[241]. Similarly, caregiver social support may affect child stimulation, and has previously also been associated with early child growth[241]. Finally, nurturing factors such as the caregiver-child relationship and discipline score may both impact child cognitive and psychosocial function[323]. In conclusion, LASSO-GEE suggested that all the measured contemporary covariates had plausible associations with the principal components. It should also be noted that the five PCA components only represent 61% of the variance in the dataset. However, overall this analysis suggests that environmental, child, caregiver and nurturing conditions measured contemporaneously have a significant impact on child growth and function, without performing multiple individual comparisons.

4.4 4.4 Discussion and Summary

This chapter has presented data from 990 children born to HIV-negative mothers who were measured using the SAHARAN toolbox, with a contemporaneous caregiver questionnaire. Measures of child function have been compared to published data and plausible differences with child sex have been described.

The better cognitive function in girls suggests this cohort has not experienced a significant level of gender-related barriers to girls' school participation, which is often experienced in low and middle-income countries[324]. However, the whole cohort were in a region that had experienced considerable disruption due to COVID-19[325] and had varied school exposure ranging from 0 to 5 years. It is well documented that girls have improved early language development compared to boys, but these differences are subtle and usually not obvious by primary school age[326]. Better cognitive function and schooling amongst girls has been observed in similar settings in Malawi and

South Africa in communities with high HIV prevalence[327], although the 990 children evaluated for MPI in this chapter were born to mothers without HIV. It is postulated that there may be a cultural element driving girls to concentrate more in school. Alternatively, girls may have some aspects of more resilience within schooling, however these concepts are difficult to measure and define[328]. Both of these theories could be examined with further investigation, for example by qualitative interviewing of caregivers and teachers, as well as direct cognitive tests that measure concentration such as the Test of Variables of Attention (TOVA) which has been previously used in Africa[329].

Internal consistency within growth and cognitive domains has been demonstrated in this chapter, although this was less obvious for the physical domain. Plausible associations between child growth and cognitive and physical function have been shown. An unsupervised principal components analysis of the entire dataset revealed five principal components which loaded particularly on growth, cognitive, physical/body composition, blood pressure, and phase angle domains respectively, to explain 61% of the variance in the dataset. Hierarchical clustering revealed four clusters, with one small cluster showing optimal growth and function. Cluster 3 demonstrated an intriguing prioritisation of cognitive function, possibly due to a higher proportion of females combined with greater caregiver education. A LASSO-GEE revealed that all contemporary factors measured contributed to the five principal components in plausible ways. Overall, the dataset confirmed plausible values and associations. Therefore, the next chapter will investigate the associations between early-life exposures and school-age growth and function.

5 Chapter 5: Associations between early-life conditions and school-age outcomes

5.1 Introduction

Hypotheses tested

This chapter tests the hypothesis that early-life growth faltering is negatively associated with school-age growth, cognitive and physical function. Secondly it tests the hypothesis that catch-up growth enables a gain in physical but not cognitive function. Finally, it tests the third hypothesis that early-life household, maternal and nurturing exposures are associated with school-age growth, cognitive and physical function.

Importance of early-life growth and environment

Children's growth and environmental conditions in early-life have long-term effects on later growth status[54] and function[13,152]. The associated benefits of catch-up growth remain highly controversial within nutrition literature because they provide insight into other windows for intervention beyond early-life[100]. Catch-up growth also provides insight into the limitations of a focus on growth at the expense of understanding broader child development and function[330].

Baseline factors of the mothers were compared within the SHINE trial between those recruited into SHINE follow-up and those who were not enrolled. This determined how representative the SFU sample was of the wider SHINE cohort. This chapter then explores the following early-life exposures:

1) Association of early-life growth status on SAHARAN outcomes
2) Catch-up growth, differentiated by child sex
3) Association of catch-up growth on SAHARAN outcomes
4) Associations of early-life environmental exposures with SAHARAN outcomes (as defined by the principal components analysis

Overall, this chapter describes how the early-life measurements of 1000 children enrolled into the SHINE Follow-up (SFU) cohort are associated with school-age outcomes derived from the SAHARAN toolbox assessment battery.

5.2 Methods

Baseline characteristics of SFU compared to the broader cohort

Baseline comparisons between children and households who were enrolled in the SHINE Follow-up (SFU) cohort and those who were not, determined how representative the substudy population was of the original SHINE cohort. All SFU children enrolled were from Shurugwi district, whilst the original SHINE trial also included the adjacent Chirumanzu district. Comparisons were divided into household, maternal and child variables. Baseline characteristics between those enrolled into and those not enrolled were compared using multinomial and ordinal regression models while handling within-cluster correlation with robust variance estimation, and Somers' D for medians with an inter-quartile range quoted (eg for household occupants), see Appendix Table A5-1).

Exploring early-life growth status and SAHARAN outcomes

It is hypothesised that early-life growth faltering is negatively associated with school-age growth, cognitive and physical outcomes. As an exploratory analysis, associations with all SAHARAN outcomes were examined, to explore the general trends illustrated by chord diagrams, similar to chapter 4.

As SHINE was a birth cohort, detailed anthropometry measurements were performed from birth until the trial interventions finished at 18 months. Child measurements both at baseline and at 18 months were used as exposure variables of growth status in models of child function at age 7 years. Birthweight was the earliest weight recorded, but due to inaccurate measurement of length at birth, the earliest usable length was measured at 1 month of age. For mid-upper arm circumference (MUAC) and head circumference, 3 months was the earliest timepoint with available data. Associations between early-life growth and 7-year outcomes were investigated using generalised estimating equations (GEE), with an exchangeable working correlation structure. As in previous chapters, the initial GEE model was unadjusted; subsequent adjusted analyses included trial factors (e.g. study nurse) and covariates selected from Directed Acyclic Graphs (DAGs) developed using Dagitty (https://dagitty.net) (see Appendix 5.8, Fig A5-1). The final model for exploring the effect of early-life anthropometry on 7-year growth and function included the following covariates: trial arm, sex, study nurse, ambient temperature at the time of the visit, date measured, breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, facility birth, maternal height and maternal schooling. For birthweight, the DAG was adjusted (see appendix Fig A5-2) so that the model used included trial arm, sex, study nurse, ambient temperature, date measured, breastfeeding duration, length-for-age Z score at 18 months, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, facility birth, maternal height, and maternal schooling.

Chord diagrams were used to explore associations between early-life growth and the SAHARAN toolbox outcomes, using standardised variables. Chord diagrams were constructed using Datagraph (Datagraph) with supporting tables shown in the appendix. For clarity, only those associations that remained significant in adjusted models were plotted in the chord diagrams. The purpose of the chord diagrams was to observe general trends associated with different aspects of early-life growth. The width of the lines in the chord diagrams are proportional to the magnitude of the association, using the same scale as in Chapter 4 to aid comparison across contemporary and early-life growth effects.

Exploring catch-up growth and school-age growth and function

It was hypothesised that catch-up growth would provide a benefit in physical but not cognitive function. Catch-up growth was defined in multiple ways. The prevalence of stunting was used with a height-for-age Z-score more than two standard deviations below the WHO median (HAZ < -2). This reflects the proportion of children most affected by linear growth failure. Similarly, the proportion of children who were underweight was defined by a weight-for-age Z-score more than two standard deviations below the WHO median (WAZ < -2)[331].

Growth was assessed using different approaches. Firstly, it was defined as the difference between 18-month and 7-year height (△HAZ) and weight (△WAZ) Z-scores, hence these were also calculated. This describes a child's growth in comparison to the WHO growth standards between 18 months and 7 years[265] . However, the absolute width of Z-scores increases with age, providing a challenge of relating a change in Z-score (△Z) to an absolute increment in height compared to a median value. Therefore, the height-for-age difference (HAD) or weight-for-age difference (WAD) was also calculated at each time point. These were obtained by subtracting the height or weight measured from the 'ideal' (median) value at that age[265], specific for each child sex[330]. The change in difference from the median for height (△HAD) and weight (△WAD) was also calculated to describe a child's growth in absolute terms compared to the median growth on the WHO charts.

Conditional growth was also explored for absolute differences, by calculating residuals from the regression analysis between the two time points at 18 months and 7 years. Conditional growth is most valuable for understanding the variability of growth within a cohort; it acknowledges that a small child at baseline has different potential to be a given size later on compared to a large child. So conditional growth explores how did children caught up compared to others who had the same baseline size.

Associations between catch-up growth in Z-scores (△HAZ and △WAZ) and 7-year outcomes explored the impact of catch-up growth. This was undertaken using four different models, using a similar approach to previous analyses. Model 1 adjusted for SHINE trial arm. Model 2 adjusted for trial factors: trial arm, sex, study nurse, calendar age recruited, ambient temperature at the time of the assessment, and age of child. Model 3 adjusted for contemporary factors (similar to Chapter 4): child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), caregiver social support score, household adversity score, number of children's books in the home, caregiver years of schooling, and caregiver gender norms score. Model 4 adjusted for trial factors plus the following baseline covariates: breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, facility birth, maternal height, and maternal years of schooling.

Exploring early-life environmental factors with SAHARAN outcomes

To restrict the number of comparisons, the association of baseline exposures with the principal components analysis (PCA) of SAHARAN outcomes was explored (see methods in Chapter 4). Previously, contemporaneous exposures were explored on SAHRAN PCA outcomes (Chapter 4). For this chapter, the exposures were baseline maternal and environmental variables on SAHARAN PCA outcomes. Again, each of the five principal components representing SAHARAN outcomes had a 10-fold cross validation with the least absolute shrinkage and selection operator (LASSO) on generalised estimating equations (GEE). The lambda tuning parameter was obtained to identify those variables that could be discarded for each principal component.

5.3 Results

Comparison between those enrolled and not enrolled into SFU

Baseline characteristics of households who were enrolled or not enrolled into the SHINE follow-up (SFU) study were broadly comparable (Appendix Table A5-1). There were no differences in household wealth quintiles, electricity, or sanitation. Households enrolled in SFU collected a slightly lower volume of water at baseline (median 6.7 litres compared to 7.5 litres), although a higher proportion of SFU households had an improved water source (68.7% compared to 61.5%). SFU households had a slightly higher proportion of livestock observed inside the house (40.5% compared to 36.0%) but also a higher number of handwashing stations at the household (11.5% compared to 8.1%). SFU compared to non-SFU households also had a slightly lower coping strategies index (median 0 (IQR 0, 6) vs 1 (IQR 0,7), respectively), suggesting marginally improved food security. However, households were similar overall, with only minimal differences observed.

For mothers (Appendix table A5-2), there was a marginally higher pregnancy mid-upper arm circumference of 26.6cm (SD 3.3) in SFU vs 26.3cm (SD 3.0) in non-SFU. This highlighted that there was little difference in nutritional status during pregnancy. SFU mothers did have higher baseline gender norms attitudes (median 2.3, IQR 1.5, 3.0) compared to non-SFU mothers (1.7, IQR 1.5, 3.0), which could plausibly lead to improved nurturing care within SFU households. Gender norms were previously observed to be associated with growth across the whole SHINE cohort[241]. Mothers also scored marginally lower on perceived social support, but this small difference was unlikely to be meaningful.

For SFU versus non-SFU children (Appendix Table A5-3), there were marginally higher rates of institutional delivery (91.4% vs 88.2%), and lower weight-for-height Z-score at 18 months, although the difference was minimal (0.1 (SD 1.1) vs 0.0 (SD 1.0)). Similarly, there were slightly higher mid-upper arm circumference Z-scores in SFU versus non-SFU children at 18 months (0.1

(SD 0.9) vs 0.0 (SD 0.9)) which was unlikely to be clinically meaningful. Overall, baseline characteristics between those recruited into SFU and the remainder of the SHINE cohort were remarkably similar. This was reassuring as it suggested that SFU children were representative of the whole SHINE cohort. Given that SHINE was a birth cohort, the next step was to investigate the associations between early-life growth and school-age growth and function.

Associations between early-life growth and school-age growth and function

The SHINE trial cohort had detailed growth measurements in the first 18 months, including length, weight, mid-upper arm circumference (MUAC) and head circumference. This enabled the associations between early-life growth and 7-year outcomes to be explored for children in the SFU cohort. Chord diagrams showed the relative magnitude of associations from adjusted models between standardised early-life measurements and standardised 7-year outcomes.

Early-life linear growth associations with SAHARAN outcomes

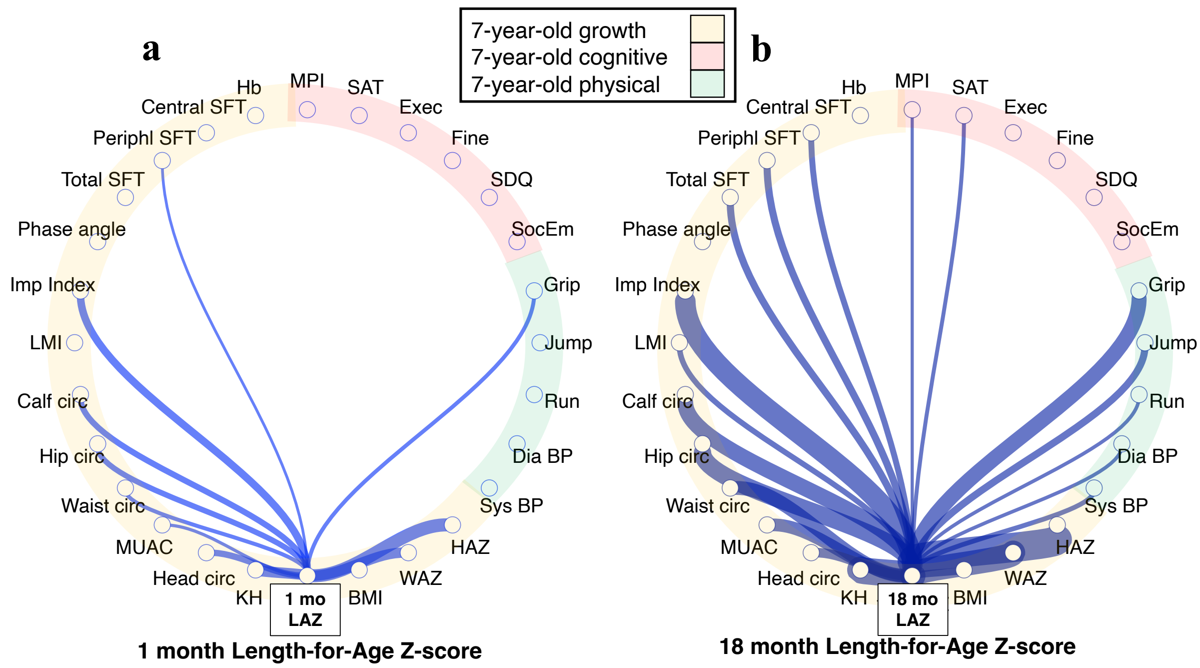


Figure 5-1 Chord diagrams of early-life length associated with SAHARAN outcomes

Chord diagrams of standardised coefficients from adjusted models showing associations of school-age growth, cognitive and physical function with a) 1 month Length-for-age Z-score (1 mo LAZ) and b 18 months length for age Z-score (18 mo LAZ). Note that the relative width of the line is in proportion to the effect size for early-life and growth by school-age. Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years.

Length-for-age at 1 month of age (1 mo LAZ) was associated with school-age height, weight and body mass index (BMI) as expected. This demonstrates the association of antenatal linear growth status with later growth trajectories[332] (Figure 5-1, table A5-4). Measures of 1 month length were also associated with school-age lean mass such as impedance index and body circumferences [278]. Interestingly, 1 mo LAZ had a small association with school-age peripheral skinfolds, but not with central skinfold thickness. The previous chapter suggested peripheral fat may be more beneficial for longer-term function, and may even be protective for cardiovascular disease[278]. Central adiposity may be more associated with immune function and later inflammation[333]. Also of note is the association between early-life length and subsequent handgrip strength, suggesting growth by early infancy may influence later school-age physical function. This highlights the importance of antenatal growth for lean mass, peripheral fat and later function. Similar associations were observed when comparing the 103/542 (19%) children who were stunted at 1 month (1 mo LAZ < -2) compared to those who were not (Table A5-5). Stunted children at 1 month had reduced functional scores at age 7 years, but there was only strong evidence of difference for measures of linear growth and impedance index. Again, central skinfolds in children who had been stunted at 1 month were relatively spared (-0.2cm) compared to peripheral skinfolds (-0.7cm). However, there was no evidence that peripheral skinfolds were smaller at 7 years, which may also suggest some catch-up in subcutaneous peripheral fat in children with early-life stunting. As expected, little catch-up in early-life height was observed: 63/102 (62%) of children who were stunted at 1 month were also stunted at 18 months (see Appendix Table A 5-6). 1 month LAZ therefore provides important insights into prenatal growth which often sets early-life growth trajectories, and highlights how crucial the antenatal period is to achieve healthy postnatal growth[334,335].

Length-for-age at 18 months (18 mo LAZ) demonstrated much larger associations with school-age growth including HAZ, WAZ, BMI and body circumferences (Figure 5-1, table A5-7). The largest standardised association measured was between LAZ at 18 months and HAZ at 7 years. These larger associations would be expected given that the later time-point provides more information on prior growth trajectories, and reflects the child's response to a range of environmental conditions in early-life. Stunting has the highest incidence at 0-3 months[24] with prevalence worsening until around the age of 2 years when growth trajectories become canalised[54]. Interestingly, there was a small association between 18 mo LAZ and 7-year lean mass index, even though LMI corrects for height, suggesting a beneficial effect of early life linear growth on lean mass in addition to increased height. 18 mo LAZ was also associated with peripheral, central and total skinfolds. This suggests that both central and peripheral subcutaneous fat accumulation by 18 months were associated with skinfold thicknesses by 7 years. There were small associations between18 mo LAZ and cognitive function (Mental processing index and School achievement test), which may reflect improved cognitive function in response to better early-life environmental conditions. Associations were much stronger for physical function, particularly grip strength and broad jump. This was consistent with the strong associations previously observed between 7-year growth and physical function in Chapter 4. The small association between 18 mo LAZ and cardiovascular fitness at 7 years likely represented the contribution of lean mass (captured within LAZ) to cardiovascular fitness. Similar results were obtained for the 290/981 (30%) children who were defined as stunted at 18 months (LAZ < -2, table A5-8). Children who were stunted at 18 months broadly scored worse on all 7-year measures, with strong evidence of difference for all strength and cardiovascular fitness tests, and for all measures of growth except for lean mass index (which corrects for height) and phase angle. Hence there were clear associations between early-life growth status and school-age growth and physical function, and smaller associations for school-age cognitive function. The next stage was to examine the association between early-life head circumference (as a measure of brain growth) and 7-year cognitive function.

School-age associations with early-life head circumference

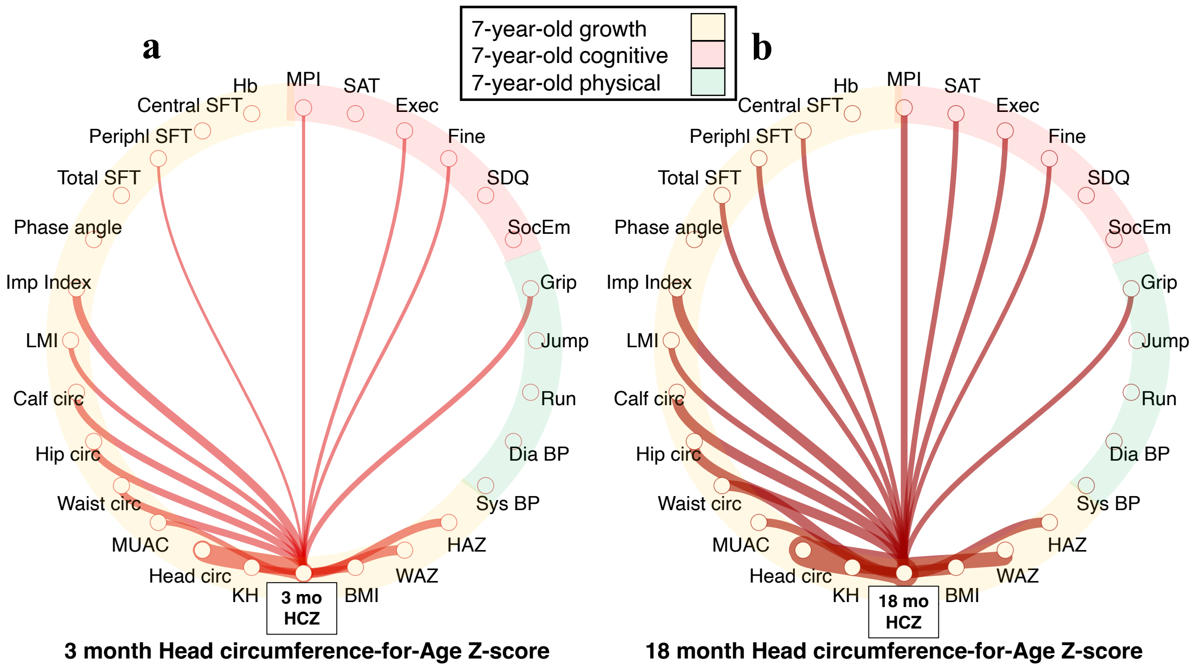


Figure 5-2 Chord diagrams of early-life head circumference associated with SAHARAN outcomes

Chord diagrams of standardised coefficients for adjusted models showing associations of school-age growth, cognitive and physical function with a) 3 month head circumference-for-age Z-score (3 mo HCZ) and b 18 months head circumference for age Z-score (18 mo HCZ). Note that the relative width of the line is in proportion to the effect size for early-life and growth by school-age Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years.

Head circumference at 3 months (3 mo HCZ) was significantly associated with 7-year growth including anthropometry, body circumferences and lean mass measures (Figure 5-2, table A5-9). It is accepted that head circumference growth is particularly important in the first 2 years of life[286]. In addition to representing early-life growth, head circumference may also be relatively protected by the body, which is in keeping with the Barker hypothesis[336]. Of note, 3 mo HCZ was also associated with peripheral skinfolds, further corroborating the importance of growth in peripheral fat at this young age. HCZ at 3 mo was also associated with 7-year grip strength, suggesting an association between head circumference and lean mass may provide a benefit in physical function. In contrast to early-life length, 3 mo HCZ was associated with cognitive function at 7 years, including cognitive processing as shown by the mental processing index (MPI), executive function from the Plus-EF total score, and fine motor function. In high-income settings, prenatal brain growth may also be causally associated with school performance, as demonstrated by a longitudinal cohort study of 500,000 children in Denmark[337]. Associations were weaker for the association between 3 mo HCZ and SAT score, but this could be because child literacy and numeracy were likely the most sensitive to varied schooling exposure within the SHINE follow-up cohort. Taken together, these findings suggest that antenatal and very early-life brain growth is important for later cognitive function.

As expected, stronger associations were seen between 18-month head circumference (18 mo HCZ) and all measures of 7-year growth and also grip strength (Table A5-10). The association between head circumference and grip strength has rarely been examined in children. However, a relationship between increased grip strength and improved brain health in old age[338] has been observed, as well as greater brain volumes and reduced frailty in cognitively impaired adults[339]. This potentially suggests that the quality of early-life growth in lean mass and brain size continues to contribute to resilience observed into old age.

18 mo HCZ was associated with all tests of directly measured cognitive function, including literacy and numeracy as measured by the SAT. This

suggested the importance of the canalised brain growth by 18 months that continues to reflect school-age brain structure and function, as well as later in adolescence[340]. Globally, the INTERGROWTH study in multiple countries has shown remarkably similar antenatal and postnatal growth of head circumference for children with good nutrition[341]. However, head circumference is also highly affected by differences in nutrition; a separate systematic study within 55 countries of multiple national and ethnic groups showed wide variations in head circumferences up to 5 years when compared to the WHO growth standards[342]. Anthropometrically the effect of reduced brain growth and function is reflected by reduced head circumference[343-345] or more recently by brain size as measured by MRI [346]. Therefore it remains highly plausible that early-life head circumference would reflect brain growth and hence be associated with school-age cognitive function. The next step was to examine associations between early-life weight and 7-year outcomes.

5.3.2.3 Birthweight and early-life weight for age (WAZ) associations with School-age growth, cognitive and physical function

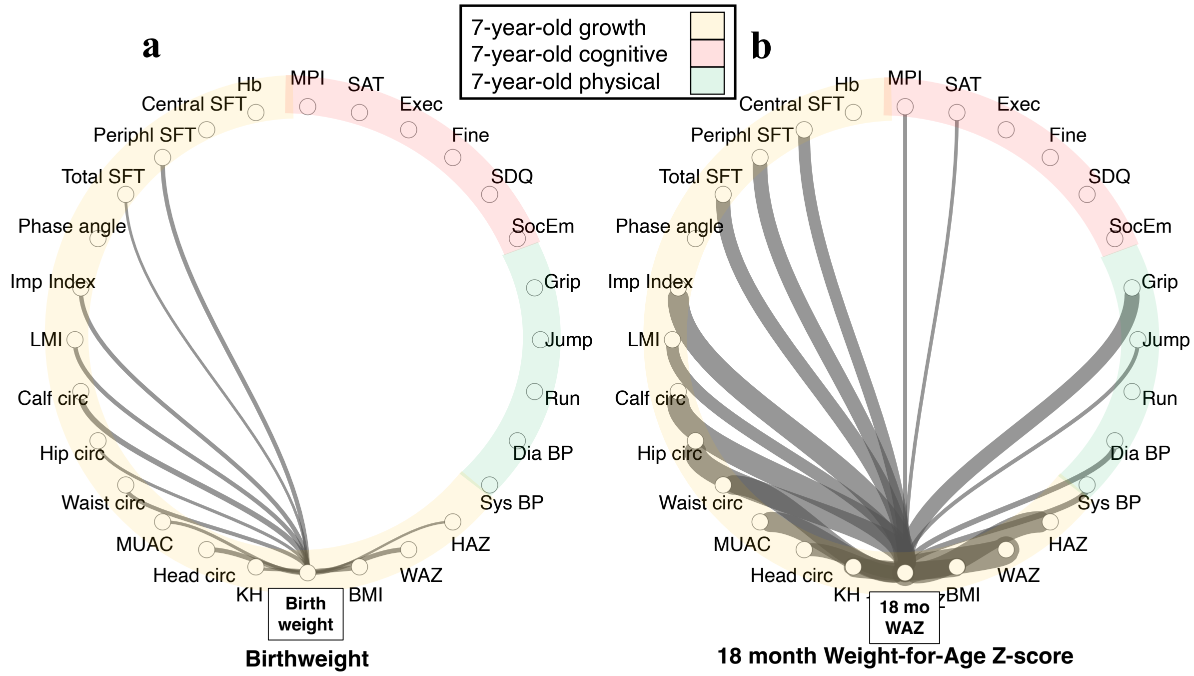


Figure 5-3: Chord diagrams of early-life weight associated with SAHARAN outcomes

Chord diagrams of standardised coefficients for adjusted models showing associations of school-age growth, cognitive and physical function with a) birthweight and b) 18 months weight for age Z-score (18mo WAZ). Note that the relative width of the line is in proportion to the effect size for early-life growth and growth by school-age. Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years.

Birthweight had plausible associations with school-age height, weight and body circumferences (Figure 5-3, table A5-11). Birthweight was associated with school-age impedance index, representing lean mass, and also with lean mass index, suggesting a contribution of birthweight to lean mass that is independent of linear growth. This was expected as birthweight is a strong predictor of lean mass, with a weaker association with later fat mass[347]. Birthweight has consistently shown associations with later muscle strength across multiple studies, as observed in a systematic review and meta-analysis[348]. For the SHINE follow-up cohort, associations between birthweight and grip strength were observed in unadjusted models (see appendix table A5-11). However, there was no evidence of difference in adjusted models which included early-life anthropometry (18 month LAZ) as covariates (see appendix Figure A5-2). This effect of body size as the causal pathway relating birthweight to grip strength has previously been observed in a UK cohort[349]. Therefore it remains plausible that the association between birthweight and grip strength is mediated through subsequent growth.

Additional insight was obtained by comparing the 87 infants who were born low birthweight (LBW, ie under 2.5 Kg) to 856 infants born above 2.5 Kg (see appendix table A5-12). Across all measures there some evidence that children who had been born LBW were performing less well. Birthweight was previously shown to be a protective factor in child development in the Drakenstein Child Health Study[318]. Overall in the SHINE Follow-up cohort, those born LBW scored lower across all cognitive tests, although there was weak evidence of difference in adjusted models. There was stronger evidence that children born LBW performed worse in the broad jump, potentially suggesting reduced physical function. This was supported by significant reductions in both lean mass and impedance indices. Skinfold thicknesses were relatively preserved for LBW children, particularly central skinfold thickness. This was consistent with literature suggesting LBW children preserve fat, with reduced lean mass[36], whilst LBW children are also at increased risk of central obesity in later childhood[350].

Only 20/86 (23%) children had both a low birthweight and were still underweight by 18 months (see appendix table A5-13), despite a similar proportion with LBW (7.8%) as those with early-life stunting (10.1%). Similarly, only 15/52 (28.8%) of those underweight (WAZ < -2) at 1 month remained underweight by 18 months (Table A5-14). This suggested that children responded to their postnatal environmental conditions, with some LBW children showing catch-up growth, whilst other children lost weight. Similar trajectories of growth faltering over the first 18 months have been observed globally[54].

18 months weight-for-age Z-score (18 mo WAZ) had strong associations with school-age growth including anthropometry, body circumferences and body composition (Figure 5-3, Table A5-15). Weight encompasses both fat mass (as was shown by strong associations with all school-age skinfold measurements) and lean mass (hence associations with school-age impedance and lean mass indices). There were also associations between 18-month weight and 7-year cognitive function (MPI and SAT), similar to those seen for 18-month length, which were likely due to the strong correlations of weight with length (Table 4-5). There were also similar magnitude associations between 18-month weight and both handgrip strength and broad-jump distance at 7 years, again reflecting the contribution of weight to lean mass. By contrast, there was no association between 18-month weight and 7-year cardiovascular fitness (Figure 5-3, Table A5-15), since weight also includes fat mass. Fat mass was shown at 7 years to be negatively associated with cardiovascular fitness (see Chapter 4). For both weight and length at 18 months, there was a small association with increased blood pressure, likely

representing the required increase in blood pressure with increasing child size[351].

Comparing the 86 children who were underweight at 18 months (defined as weight-for-age Z-score < -2) to the 895 children with WAZ > -2 revealed similar associations to WAZ at 18 months (appendix table A5-17). Of note, there were no significant associations for underweight children with reduced cognitive function, although head circumference was also slightly reduced in those underweight at 18 months. However, for physical function, both grip strength and broad jump were significantly reduced, likely reflecting reduced lean mass as seen by lower impedance and lean mass indices. Cardiovascular fitness was not significantly reduced, probably because of a reduction in fat mass which was negatively associated with shuttle run performance (see chapter 4). Underweight children have previously been noted to be agile in endurance tests in South Africa and Ghana[313]. Underweight at 18 months was associated with reductions in school-age peripheral and central skinfolds, potentially suggesting that challenging early-life nutrition conditions continued. Weight is the least canalised metric and hence most responsive to contemporary conditions[352]. In SFU, underweight children at age 18 months appeared less able to have catch-up in fat mass by 7 years, compared to those with initial low birthweight. Overall, early-life weight showed similar associations as early-life length, with a few differences, partly explained by length having a stronger relationship to lean mass, whilst weight includes both fat and lean mass. The final part of this section examines the association between early-life mid-upper arm circumference (MUAC) and school-age growth and function.

Mid-upper arm circumference (MUACZ) associations with school-age growth, cognitive and physical function

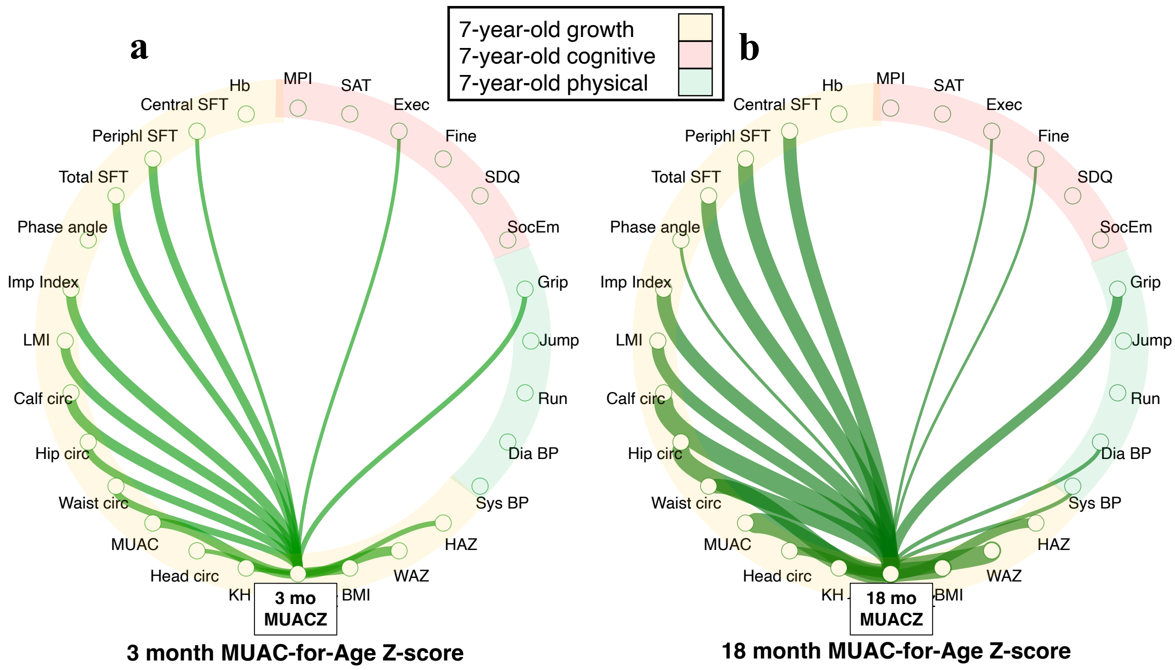


Figure 5-4 Chord diagrams of early-life MUAC associated with SAHARAN outcomes

Chord diagrams of standardised coefficients from adjusted models showing associations of school-age growth, cognitive and physical function with a) 3-month Mid-upper arm circumference for age Z-score (3 mo MUACZ) and b) 18 month Mid-upper arm circumference for age Z-score (18 mo MUACZ). Note that the relative width of the line is in proportion to the effect size for early-life growth and growth by school-age. Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years

Mid-upper arm circumference Z-scores (MUACZ) represent a measure of both lean and fat mass in the arm that can be used for monitoring responsiveness to nutrition programs[353]. Therefore it was expected that MUAC Z-score at 3 months (3mo MUACZ) would have associations of a similar size as weight and height with school-age measures of anthropometry, body circumferences, fat and lean mass (Figure 5-4, Appendix table A5-17). Impedance and lean mass indices had associations of a similar size, showing how MUACZ may also associate with lean mass, independent of length. MUACZ at 3 mo also had stronger associations with school-age peripheral compared to central skinfolds, consistent with early-life growth appearing to guide peripheral more than central fat accumulation. 3 mo MUACZ was also associated with grip strength, which suggested it may reflect early lean mass development in the arm. 3 mo MUACZ had a small association with school-age executive function, which may reflect a benefit in reaction speed, and suggests potential benefits of early-life lean mass and peripheral fat on later brain function. In multiple studies among children with severe malnutrition, there is clear evidence that undernutrition (represented by low MUAC in early life) has long-term cognitive impacts even after nutritional rehabilitation[354]. However, this was not observed in the SHINE Follow-up cohort since only 20/990 children had a documented MUAC Z-score < -2 Z-scores in any measurement from 3 to 18 months of life.

Consistent with early-life length, head circumference and height, there were strong associations between 18 mo MUACZ and school-age growth and body composition. Central skinfold thickness was also strongly associated with 18mo MUACZ, suggesting central subcutaneous fat accumulation occurred after 3 months. Interestingly 18 mo MUAC was also associated with fine motor coordination, which was consistent with the reaction speed and skills measured in executive function, since the Plus-EF test also relied on fine motor coordination. 18 mo MUACZ also had a stronger association with subsequent grip strength than at 3 months. Therefore growth in early-life MUACZ may shape development in later arm strength and coordination. There was also a small association with increased diastolic and systolic blood pressure, likely reflecting an increased body size requiring higher blood pressure for blood circulation.

Overall, these findings provide strong evidence to support the hypothesis that early-life growth faltering affects later school-age growth, body composition, physical and cognitive function. Early-life length and weight associate most strongly with overall growth and physical function at age 7 years. Early-life head circumference associates most strongly with cognitive function, whilst MUAC is related to arm strength and function. The importance of early-life growth was clearly demonstrated. The next stage was to briefly examine the impact of any relative catch-up growth after 18 months within the SFU cohort.

Exploring catch-up growth by child sex

Proportions of stunted and underweight at 18 months and 7 years were calculated for girls and boys (Table 5-1).

	Girls	Boys	Risk ratio (boys, 95% CI)	p-value
Stunted at 18 months	23.8% (120/504)	35.6% (170/477)	1.4 (1.2, 1.6)	<0.001
Stunted at 7 years	2.0% (10/506)	6.2% (30/484)	2.6 (1.5, 4.6)	0.001
Underweight at 18 months	6.6% (33/504)	11.1% (53/477)	1.7 (1.2, 2.4)	0.001
Underweight at 7 years	4.0% (20/506)	7.4% (36/484)	1.9 (1.2, 3.0)	0.006

Table 5-1 Proportions of stunted and underweight in children within SHINE follow-up at 18 months and 7- years, by child sex.

Examining Table 5-1, children in the SHINE Follow-up cohort exhibited catch-up growth between 18 months and 7 years with significant reductions in numbers with stunting and underweight, with more catch-up up in girls than boys. Differences between Z-scores at 7 years and 18 months were also calculated to visualise catch-up growth in height and weight (Figure 5-5).

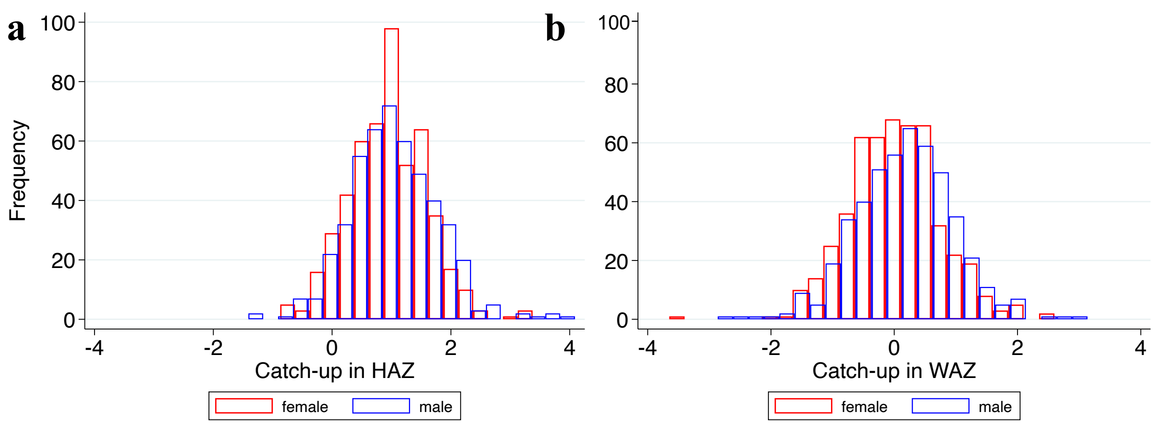


Figure 5-5 Histograms of catch-up growth

Histograms comparing catch-up in a) Height-for-age Z-score (△HAZ) and b) Weight-for-age Z-score (△WAZ) between 18 months and 7 years.

It was clear that the catch-up growth in Height-for-Age Z-score (△HAZ) occurred for both boys and girls. However, there was minimal change in weight-for-age Z-score (△WAZ) for girls, although across the cohort, boys appeared to show some catch-up in weight (Figure 5-5b). The height-for-age difference (HAD) and weight-for-age difference (WAD) from the WHO median, as well as change in absolute differences for height (△HAD) and weight (△WAD) were also calculated. Finally, conditional growth for absolute differences was also calculated (Table 5-2).

Outcome	Girls		Boys		GEE Mean difference (95% CI)		
	N	Mean (SD)	N	Mean (SD)	Unadjusted	Model 1	Model 2
Height at 7 years, cm	506	120.2 (4.9)	484	120.1 (4.9)	-0.1 (-0.8, 0.6)	-0.1 (-0.8, 0.6)	0.0 (-0.7, 0.7)
Height for age Z-score (HAZ) at 7 yr	506	-0.4 (0.8)	484	-0.6 (0.9)	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)	-0.2 (-0.3, -0.1)
Length at 18 months, cm	504	77 (2.9)	477	78 (2.9)	1.0 (0.6, 1.4)	0.9 (0.6, 1.3)	1.0 (0.6, 1.4)
Length-for-age Z-score (LAZ) at 18 mo	504	-1.4 (1.0)	477	-1.6 (1.1)	-0.3 (-0.4, -0.1)	-0.3 (-0.4, -0.2)	-0.3 (-0.4, -0.2)
Catch-up in Height Z-score from 18mo to 7yr (△HAZ)	**504**	**0.9 (0.6)**	**477**	**1.0 (0.7)**	**0.1 (0.0, 0.2)**	**0.1 (0.0, 0.2)**	**0.1 (0, 0.2)**
Height-for-age difference (HAD) at 7 yr, cm	506	-2.2 (4.6)	484	-3.2 (4.8)	-0.9 (-1.6, -0.2)	-0.9 (-1.6, -0.2)	-0.9 (-1.6, -0.2)
Length-for-age difference (LAD) at 18 mo, cm	504	-4.0 (2.8)	477	-4.5 (2.9)	-0.5 (-0.9, -0.1)	-0.5 (-0.9, -0.2)	-0.5 (-0.9, -0.1)
Catch-up in height difference from 18mo to 7yr, cm (△HAD)	504	1.8 (3.1)	477	1.3 (3.3)	-0.4 (-0.8, 0)	-0.4 (-0.8, 0)	-0.4 (-0.8, 0.1)
Conditional growth in HAD from 18mo to 7yr	504	0.1 (3.1)	477	-0.2 (3.3)	-0.3 (-0.7, 0.1)	-0.3 (-0.7, 0.1)	-0.3 (-0.7, 0.1)
Weight at.7 years, Kg	505	21.4 (3)	483	21.6 (2.6)	0.2 (-0.2, 0.6)	0.2 (-0.2, 0.6)	0.2 (-0.1, 0.6)
Weight-for-age Z-score (WAZ) at 7 yr	505	-0.6 (0.8)	483	-0.7 (0.9)	-0.1 (-0.3, 0)	-0.1 (-0.3, 0)	-0.1 (-0.3, 0)
Weight at 18 months, Kg	504	9.7 (1.2)	477	10.0 (1.1)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)
Weight-for-age Z-score (WAZ) at 18 mo	504	-0.6 (1.0)	477	-0.9 (1.0)	-0.3 (-0.4, -0.2)	-0.3 (-0.5, -0.2)	-0.3 (-0.4, -0.2)
Catch-up in Weight Z-score from 18mo to 7yr (△WAZ)	**503**	**0.0 (0.7)**	**476**	**0.2 (0.8)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**
Weight-for-age difference (WAD) at 7yr, Kg	505	-1.7 (2.9)	483	-2.0 (2.5)	-0.3 (-0.7, 0.1)	-0.3 (-0.7, 0.1)	-0.3 (-0.7, 0.1)
Weight-for-age difference (WAD) at 18mo, Kg	504	-0.6 (1.1)	477	-1.0 (1.1)	-0.4 (-0.5, -0.2)	-0.4 (-0.5, -0.2)	-0.4 (-0.5, -0.2)
Catch-up in weight difference from 18mo to 7yr, Kg (△WAD)	503	-1.1 (2.3)	476	-1.0 (2.0)	0.1 (-0.2, 0.3)	0.1 (-0.2, 0.4)	0.1 (-0.2, 0.4)
Conditional growth in absolute WAD from 18mo to 7yr	503	-0.1 (2.2)	476	0.1 (1.9)	0.3 (0, 0.5)	0.3 (0, 0.5)	0.3 (0, 0.6)

Table 5-2 Catch-up growth within the SFU cohort

Height at 7 years, length at 18 months, weight and relative catch-up growth measurements for the SHINE Follow-up cohort. Catch-up in height and weight Z-scores are highlighted in bold as these provide the basis for further investigation of their impact on 7-year outcomes (section 5.3). Model 1 adjusted for arm. Model 2 adjusted for trial factors arm, study nurse, age of child, calendar age recruited, temperature)

With increasing age, the absolute value of height or weight represented within the Z-score width increases. Therefore focusing on Z-scores may mean an absolute difference is not fully appreciated[330]. Therefore HAD and WAD provide additional insight into whether absolute growth deficits continued to accumulate, despite an apparent increase in catch-up by Z-score[355]. The relative size in growth measures is also important: between 18 months and 7 years, the mean height increased by 150%, whilst the mean weight increased by 218% (Table 5-2).

Boys and girls have almost the same absolute height by 7 years (120 cm), but when examining the WHO Z-scores by child sex, boys have a lower height-for-age Z-score (HAZ) (-0.6, SD 0.9) at 7 years than girls (-0.4, SD 0.8), as noted in Chapter 7. Both sexes had more negative length-for-age Z-scores (LAZ) at 18 months: for girls, LAZ was -1.4 (SD 1.0), and for boys -1.6 (SD 1.1). Therefore, across the whole cohort there was a considerable catch-up in Z-scores for height (△HAZ) over the 6-year period, which was marginally lower in girls (0.9, SD 0.6) compared to boys (1.0, SD 0.7). Examining the height-for-age difference (HAD) compared to the 50th percentile, revealed that girls had a lower HAD at 7 years of -2.2 cm (SD 4.6) compared to boys -3.2 cm (SD 4.6). This had improved for all children compared to the 18-month length-for-age difference: at 18 months girls had a LAD of -4.0cm (SD 2.8), and boys had a LAD of -4.5cm (SD 2.9). Hence catch-up growth reduced the height-for-age deficit (△HAD) for girls by 1.8cm (SD 3.1), compared to boys 1.3cm (SD 3.3). Corroborating this, boys also had more negative values of conditional linear growth (-0.2, SD 3.1) compared to girls (0.1, SD 3.3) over the 6-year period, reflecting lower absolute growth in boys. Conditional linear growth provides a correction for regression to the mean. Therefore it describes relative growth changes during this period within the variability of the cohort.

Boys and girls had a similar total weight by 7 years, although boys had marginally reduced weight-for-age Z-score at 7 years (-0.7, SD 0.9) compared to girls (-0.6, SD 0.8) as previously noted in Chapter 4. At 18 months, boys were slightly heavier (10.0 Kg, SD 1.1) than girls (9.7 Kg, SD 1.2), but they had reduced WAZ at 18 months (-0.9, SD 1.0) compared to girls (-0.6, SD 1.0). Hence boys demonstrated a slight catch-up in △WAZ of 0.2 (SD 0.8) whereas girls had a minimal catch-up in △WAZ of 0.004 (SD 0.7). The increasing weight of children with older age meant the absolute width within a Z-score also increased; therefore, although the deficit in WAZ was reduced from 18 months to 7 years, the weight-for-age difference (WAD) deficit *increased* to -1.7 Kg (SD 2.9) for girls and -2.0 Kg (SD 2.5) for boys at 7 years, compared to WAD scores at 18 months of –0.6 Kg (SD 1.1) for girls and -1.0 Kg (SD 1.1) for boys. Therefore, catch-up growth was defined by change in Z-scores to avoid the effect of increasing absolute deficits. For conditional growth in absolute values, there was a slight increase in weight for boys (0.1, SD 1.9) over the 6-year period compared to girls (-0.1, SD 2.2).

Conditional variables represent the child's deviation from the expected size using their own previous measures and the growth of the other children in the cohort[109]. This can then be interpreted as representing faster or slower relative linear growth or weight gain[109]. Positive residuals represent children who grow above the expected regression calculation, and negative residuals are those who grow below this. For example, a child with a positive value of conditional height at 7 years is taller and thus had a faster rate of linear growth over the time period[109]. In table 5-2, girls had improved conditional growth in HAD and boys had improved conditional growth in WAD, which reflected their relative improvements in △HAD and △WAD, respectively.

Overall, the whole cohort exhibited considerable catch-up linear growth (△HAZ) of around 1 Z-score from 18 months to 7 years, with girls demonstrating a slightly higher improvement in △HAZ. This was also reflected in improved height-for-age difference (HAD) and conditional growth for girls more than boys. By contrast, for weight there was only a small improvement in Z-score (△WAZ) in boys, whilst girls had a negligible improvement. These small increases in △WAZ meant both girls and boys had a small increase in the absolute weight-for-age deficit (WAD) from 18 months to 7 years. Boys had slightly increased conditional growth in WAD compared to girls. The next section therefore examines the associations of this catch-up in linear growth (△HAZ) and marginal gain in weight (△WAZ) on 7-year growth and function.

Associations between catch-up growth and school-age growth and function

The impact of catch-up growth as defined by change in height Z-score (△HAZ) and change in weight Z-scores (△WAZ) was initially calculated for the whole cohort (Table A5-19, 20, figure A-3). However, given the variability in catch-up growth with child sex, the analysis focused on △HAZ and △WAZ split by child sex (Figure 5-6, Table A5-21 & A5-22)

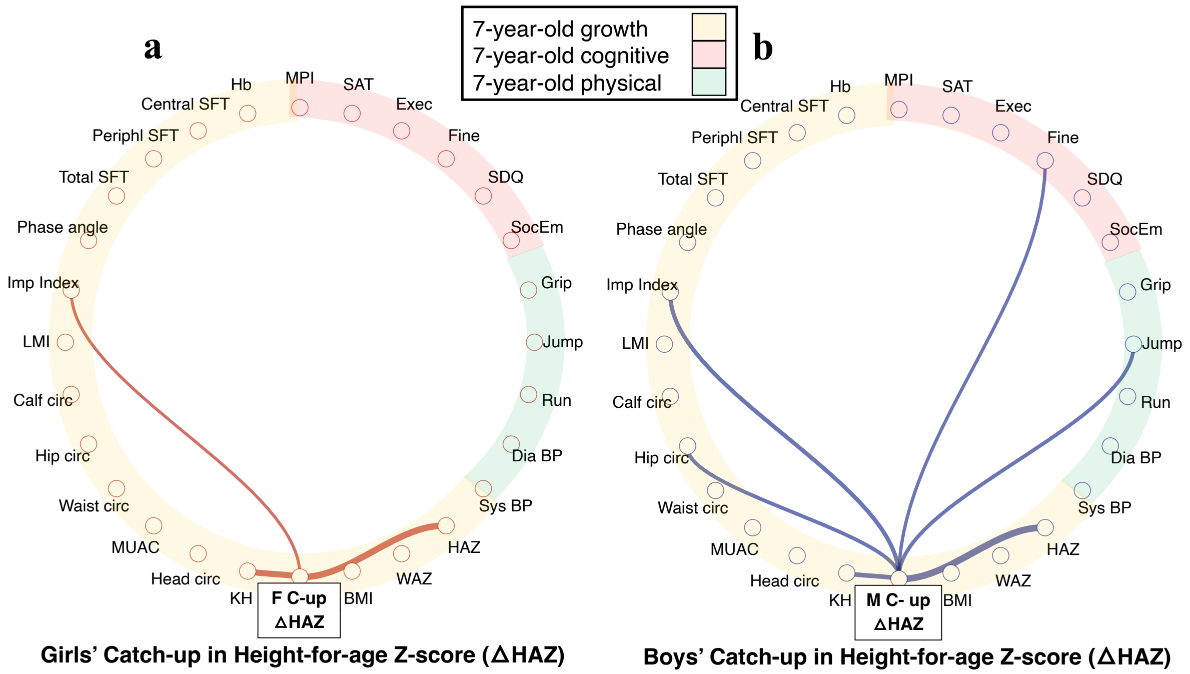


Figure 5-6 Associations of growth in HAZ from 18 month to 7 year with SAHARAN outcomes

Associations of catch-up height-for-age Z-scores (△HAZ) for girls and boys for the SHINE Follow-up cohort with 7-year growth, cognitive and physical function. Note the relative width of the line is in proportion to the effect size for early-life growth as portrayed in section 5-3-2. Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years.

As previously described, both girls and boys had demonstrated linear growth catch-up (△HAZ) of ~1 Z-score (SD 0.7) from 18 months to 7 years. This was predictably associated with HAZ at 7 years, although the association was weaker than expected. This may be because the variability from early life is driving the catch-up growth observed, again demonstrating the importance of early-life growth. As expected, catch-up growth was associated with other variables strongly correlated with linear growth such as knee-heel length and impedance index, as a measure of lean mass. Interestingly, increases in △HAZ were not associated with increases in BMI or WAZ, suggesting that linear growth did not particularly increase fat mass. Lean mass also only increased in proportion to height as shown by an increase in impedance index without any increase in lean mass index (LMI). For boys only, there was an additional association with fine motor function and broad jump length. Boys also had an increased hip circumference, which may suggest some additional gluteal muscle that would provide additional strength for the broad jump. The increase in lean mass may also have improved fine motor function in boys. Boys had previously greater rates of stunting and so this may suggest an additional small benefit of catch-up growth in those with reduced early-life growth or alternatively that boys are more able to benefit from school-age growth. Boys may be more responsive to environmental conditions, with both increased sensitivity to stunting and also ability to benefit for improved environmental conditions[356]. This is likely due to a complex interaction of social, environmental, and genetic factors throughout life[356].

The associations with catch-up weight gain in Z-score was also examined (△WAZ) (Figure 5-6, table A5-23 & A5-24).

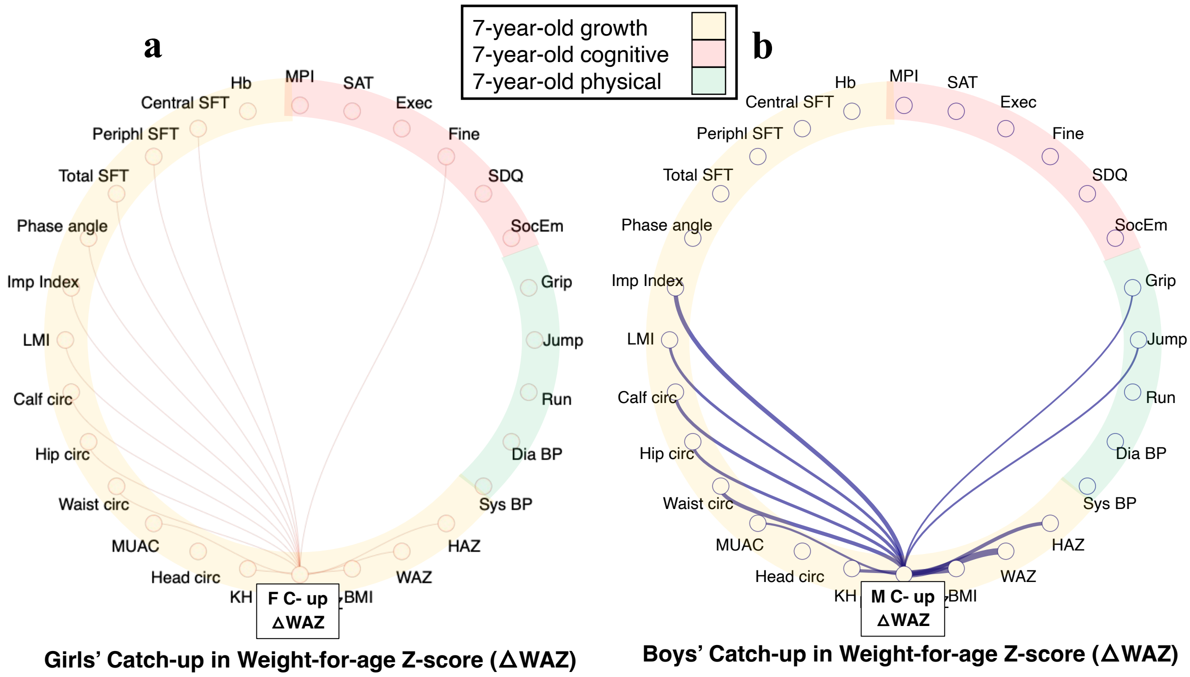


Figure 5-7 Associations of growth in WAZ from 18 month to 7 year with SAHARAN outcomes

Associations catch-up weight-for-age Z-scores (△WAZ) for girls and boys with 7-year growth, cognitive and physical function for the SHINE Follow-up cohort. Note the relative width of the line is in proportion to the effect size for early-life growth as portrayed in section 5-3-2. Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years

Girls had a negligible catch-up in △WAZ, which was associated with minimal increases in growth parameters, which are unlikely to be clinically meaningful. By contrast, boys demonstrated a higher △WAZ, which was associated with increased BMI, HAZ, knee-heel length and body circumferences. As expected, there was no association with head circumference, since the majority of head circumference growth occurs in the first 2 years[340]. The increase in △WAZ was mainly associated with increased lean mass (both impedance and lean mass indices). There was no significant increase in fat mass as measured by skinfold thicknesses, suggesting that increased body circumferences may reflect lean mass accrual. This was corroborated by small functional improvements in boys' grip strength and broad jump.

This again suggested a small benefit for boys in school-age catch-up growth[356]. However, the improvement in fine motor function, previously seen with △HAZ, was not seen for △WAZ. This may suggest different pathways of benefit in catch-up growth for height when compared to weight, or alternatively may reflect their marginal nature given all benefits were small in magnitude.

This section has shown that catch-up within the SHINE cohort in △HAZ of around 1 Z-score is present in both girls and boys, although a small functional benefit was only observed in boys for fine motor function and broad jump. Chord diagrams have demonstrated the majority of observed HAZ by 7 years was dependent on the variability within the first 18 months, with only a small proportion attributable to later catch-up growth. Catch-up △WAZ of 0.2 was observed in boys only, which was associated with increased lean mass, BMI, body circumferences and small improvements in hand grip strength and broad jump distance. Examining the hypothesis that catch-up growth would provide benefits in physical function, (△HAZ and △WAZ), the effect size observed was very small. Catch-up growth also only appears to provide a benefit in boys. Early-life growth status appears to have more substantial associations with later function. Given the importance of early-life demonstrated in previous sections, the final section in this chapter examines the impact of early-life environmental factors.

Associations between early-life environmental and maternal factors and school-age growth and function

This section aimed to test the hypothesis that early-life environmental exposures were associated with school-age growth and functional outcomes. Given the differences in growth with child sex, it was first checked if there was any difference in early-life exposures between boys and girls. There were no significant differences between boys and girls for early-life environmental or maternal variables (Appendix table A5-25). Next, using the five principal components for school-age outcomes generated in Chapter 4, a LASSO GEE model was used to identify which standardised early-life variables were still associated with each PCA component. Note that the optional lambda values for early-life were generally small, so variable reduction was small in most models. This also potentially suggested that early-life variables acted on multiple outcomes.

	Principal component number	PC1	PC2	PC3	PC4	PC5
	Description of principal component	Nutritional status	Cognitive	Physical & lean mass	Blood pressure	HAZ, Phase angle
	Lambda	0.68	0.51	0.50	0.49	1.82
Study	Intervention arm					X
	Calendar date measured					
	Data collector					
	Ambient temperature					
Child	Sex	X				X
	Child age, yr			X		X
Environment	Household (HH) religion					X
	HH Socioeconomic scale			X	X	X
	Employed					X
	HH Coping strategies index (CSI)	X	X			X
	HH Dietary diversity score				X	X
	HH size		X		X	X
Maternal	Marital status					X
	Parity	X		X		X
	Maternal gender norms	X	X	X	X	X
	Maternal Social support	X	X	X	X	X
	Maternal education	X		X		X
	Maternal depression score (EPDS)			X	X	X
	Maternal BMI					X
	Maternal MUAC		X	X		
	Maternal Hb	X		X	X	X

Table 5-3 LASSO-GEE application to baseline factors

Results from the least absolute shrinkage and selection operator (LASSO-GEE) application to the, showing which baseline early-life variables remain after the lambda value is applied to each principal component. X means the variable no longer remains, so is not associated with the principal component outcome.

All early-life variables also contributed to at least one of the principal components. For child outcomes, child sex would be expected to influence all components, but surprisingly did not remain for PC1 or PC5, possibly because aspects of nutritional status were also included in the remaining components. Child age would also contribute to lean mass and physical function, although surprisingly was not included in PC3, but it was included in PC1 and PC2.

For environmental factors, it was plausible that baseline household socioeconomic scale, maternal employment and household dietary diversity all impact child growth and cognition, as was observed. Baseline socioeconomic status remained correlated with contemporary socioeconomic status and is a well-recognised risk factor for early child development[318,319]. Maternal employment may alleviate poverty, whilst dietary diversity is highly associated with household wealth, particularly in Zimbabwe[357]. The coping strategies index (CSI) detects food insecurity[320], which may have long-term impacts on a child's growth and physical function, hence it was associated with PC3. Household size may also improve ability for subsistence farming, hence improving children's growth in early years[322], although alternatively there may be increased competition for food. Maternal religion was associated with four main principal components. 454/944 (48%) of SHINE Follow-up mothers were from the Apostolic faith, which has been associated with lower socioeconomic status, reduced maternal autonomy[358] and reduced engagement with child health services[359]. Hence religion may have multiple mechanisms for a potential association with early-life child growth and later physical and cognitive function.

Baseline maternal capabilities such as maternal depression score are well recognised risk factors that may impact early-life child growth and later cognitive function [318]. Maternal education was associated with PC2 for child cognition as well as PC4. The mechanisms by which maternal education and household wealth influence child development outcomes may be multiple, including improved food insecurity and growth[318]. A recent analysis of UNICEF MICS datasets from 28 countries from 2010-2018 suggested from structural equation modelling that the predominant mechanism may be from educated mothers sending their children to early child education[360], which was in turn associated with improved early child development scores. By contrast, the direct effects of maternal education and home environment were much smaller in this analysis[360]. Maternal capabilities such as gender norms and social support did not load onto any of the five principal components, although these scales have previously shown to be associated with early child growth in this cohort[241]. This may be due to the smaller sample size of the SHINE follow-up cohort, or potentially they could associate with child outcomes over a shorter time period, as contemporary measures of maternal capabilities were associated with child nutritional status (PC1) and cognitive function by 7 years (PC2) (see chapter 4).

Maternal body mass index was associated with multiple measures of child nutritional status and function (PC1-4), likely reflecting better antenatal growth. It has been well documented that improving maternal BMI away from underweight reduces the risk of stunting[361]. Maternal underweight and obesity were rare in this cohort: only 26/856 (3%) mothers had a BMI <18.5 kg/m^2 and 71/846 (8%) had a BMI >30 kg/m^2. Maternal height is well recognised to influence child growth through genetic factors combined with ongoing environmental factors such as nutrition and poverty[44]. Maternal MUAC also reflects maternal nutrition, but interestingly was only associated with PC1 for child nutritional status and PC4 for blood pressure. This could be because maternal MUAC was highly correlated with maternal BMI (R=0.84) and only 74/979 (8%) mothers had a MUAC below 23 cm which is a cut-off for maternal malnutrition. However, maternal MUAC does remain an important marker of short-term maternal nutrition within Africa[362]. Maternal haemoglobin was associated with the principal component for cognition which was plausible, since anaemia in pregnancy is recognised as a leading risk factor for impaired child development[13]. Recent imaging studies in the Drakenstein Health Cohort in South Africa have shown that maternal anaemia in pregnancy is associated with altered brain structure in children, whereas postnatal child anaemia was not[363]. This stressed the importance of prenatal nutrition, and maternal anaemia, BMI, MUAC and height were all markers of this.

In summary, all the available early-life variables had plausible associations with the principal components representing child growth and function. Therefore this provided strong evidence to support the hypothesis that early-life environmental factors are associated with school-age growth and function. However, there were likely to be multiple other factors that were not included. For example, one analysis across multiple countries in Africa showed that it was maternity and antenatal care that had the greatest effect on child stunting[364]. This may reflect an increase in preventive services that impact maternal and child health in multiple ways including improved birth outcomes and improved nutritional status through access to deworming and iron supplementation[364].

5.4 Discussion

This chapter has highlighted the strong evidence for associations reported in other cohorts between early-life conditions and school-age growth[54] and function[13,152]. The sample of children in this follow-up study were shown to be representative of the wider SHINE cohort. Early-life length and weight had strong associations with school-age growth and physical function. Early-life length showed stronger associations with lean mass, whilst weight was associated with both lean mass and fat mass (represented by skinfold thicknesses). As expected, early-life head circumference had stronger evidence of associations with cognitive function, and MUAC associations were focused on school-age arm strength and function. 18-month measures had stronger associations with 7-year outcomes than did birthweight, because they were closer in time and reflected responses to early-life environmental conditions. Catch-up growth in height ($\triangle$HAZ) of 1 Z-score was associated with small benefits in physical function among boys only. This could be because boys had greater stunting prevalence, or alternatively because boys were more responsive to environmental conditions. Similarly boys experienced a small catch-up of 0.2 Z-scores in weight (△WAZ), associated with small benefits in physical function. An important consideration is also the consideration of COVID-19, which may have had multiple indirect impacts on socioeconomic, psychosocial and food security[325]. This potentially would have a short-term impact on weight (which is more responsive to short-term changes) than height. Further analysis could explore the effect of this catch-up growth to 7 years when including the initial values of 18 months in adjusted models, as well as contributions from regression to the mean.

Implications of early-life growth and school-age body composition

Associations between early-life growth and later body composition may be population-specific, with infant weight gain predicting subsequent lean mass in LMIC such as Zimbabwe[347]. However, this is clearly context-specific since postnatal weight gain may predict subsequent fat mass and obesity in industrialised populations and high-income settings[347]. Overall, studies of stunted children have consistently shown an ongoing deficit in lean mass by school-age or in adolescence, which may reflect ongoing functional deficits[365], such as in grip strength[38].

The relative prioritisation of central fat for children with growth faltering is a recurring theme that has been corroborated by other studies that have examined early-life body composition[277]. Gambian infants with early-life growth faltering had greater subscapular skinfold than triceps skinfold thicknesses indicating similar central fat preservation [212]. A South African study which measured body composition at 10 years showed that increased birthweight was associated with greater lean mass at age 10 years, while stunting at 1 year was associated with reduced lean mass and fat mass, and by age 2 years with reduced lean mass only[366]. This suggests some catch-up in fat mass. Similarly in Jamaica, stunted children had a more central fat distribution[277]. This has also been shown in Nepal with ongoing physiological deficits in lung function, smaller kidneys and reduced leg length[365]. Central fat may be more associated with short term survival, although the mechanism is unclear[36]. Studies in Brazil[367] and North Korea[368] have suggested stunted children have lower rates of fat oxidation, which may predispose them to fat accumulation. However, in children aged 2-6 years from Cameroon, stunted children had a similar resting energy expenditure and fat oxidation, but were less active and had reduced dietary diversity[369]. Hence there may be additional contributions beyond early-life oxidation such as contemporary diet and reduced activity that predispose stunted children towards gaining greater fat mass[369].

Despite associations between early-life growth and subsequent lean mass and peripheral fat, no associations were noted for the bioimpedance phase angle, which represents cellular tissue health. Previously in Chapter 4, phase angle was associated with school-age grip strength and broad jump (see Figure 4-4). This may suggest tissue health as measured by the bioimpedance phase angle reflects muscle development more in later life.

Catch-up growth

The description of growth by describing proportions of children with stunting or underweight does have inherent limitations[370] because there is no biological justification for this cut-off[330], which is more usefully applied to population-level data. Secondly the number of stunted children vastly underestimates the proportion affected by inadequate growth[370]. This is because the entire population is shifted downwards in populations with a prevalence of stunting above the 2.5% expected from the WHO median[330]. Therefore population changes over time were also examined using continuous scores of growth.

Z-scores provided the trajectory corrected for age and sex compared to the ideal group that represents global child growth in optimum conditions[265] . Z-scores are commonly used to describe child growth over time and the WHO trajectories form the basis of national growth monitoring. However, there are differences in growth within nations that reflect the country’s environment: using the 2018 National Nutrition survey in Zimbabwe, children were shorter and weigh less than the WHO growth standards, which may lead to overestimating stunting and underestimating obesity[371]. Difference in Z-scores revealed that children were catching up in height (△HAZ) of ~1 Z but less so in weight (△WAZ of +0.2 Z in boys only).

Height-for-age difference (HAD) and weight-age-difference (WAD) provided additional insight into whether absolute growth deficits continued to accumulate[355]. In this cohort, △HAD decreased over time due to the considerable catch-up growth in height for both boys and girls, whereas △WAD increased, due to less catch-up in weight. Conditional growth described this further showing increased growth in HAD for girls compared to boys, but increased WAD in boys compared to girls.

Catch-up in height has previously been observed in multiple cohorts, particularly in the Gambia[100], although few studies have explored its functional benefits. Although there were few observed benefits in function by school-age using absolute values of △HAZ and △WAZ, this catch-up growth may have later benefits for the adolescent growth spurt such as reducing the risk of obstetric complications in girls[372]. This catch-up growth may also provide epigenetic benefits passed onto offspring, given the association of maternal height and growth[44], as well as reducing future non-communicable disease risk. Additionally, catch-up growth can be explored in alternative ways that account for regression to the mean, by including the initial value of LAZ at 18 months in adjusted models, or accounting for the correlation between initial and final values of Z-scores[373]. In addition, the impact of conditional growth from birth to 18 months, as well as weight-for-height Z-scores could be explored in the future.

Overall, this chapter has shown how early-life growth is a major determinant of later cognitive and physical function. Early-life growth also sets the trajectories of early-life body composition: birthweight and infant length are consistently associated with subsequent lean mass and peripheral fat. Central fat seems to catch up across the cohort, probably as a key response for survival. Although catch-up growth did occur in this cohort, absolute values of △HAZ and △WAZ had little impact on school-age function, although there may be important benefits in later life. All the SAHARAN results so far presented have been for children born to women without HIV. The next chapter explores the impact of antenatal HIV exposure by comparing children born to women with and without HIV.

6 Chapter 6: SAHARAN outcomes in children who are born HIV-free

6.1 Introduction

Hypotheses tested

Chapter 6 aims to explore the impact that antenatal HIV exposure had on school-age child growth, cognitive and physical function for children born HIV-free (CBHF). The main hypothesis tested was that CBHF would demonstrate reduced cognitive function by age 7 years compared to children born to mothers without HIV (CHU). Additional hypotheses tested were that CBHF also had reduced growth and physical function compared to CHU.

This chapter briefly describes the importance of CBHF, and then describes the statistical methods to compare CBHF with CHU, including models that adjusted for contemporary or baseline factors. In the results section, comparisons are made for CBHF that were enrolled into SHINE follow-up (SFU) with those not enrolled. The main aim is the comparison between CBHF and CHU for SAHARAN toolbox outcomes. A further detailed secondary analyses of subtests is described as well as a sensitivity analysis exploring the interaction with child sex. Finally, the implications of these results are discussed.

Importance of measuring children born HIV-free (CBHF)

In 2021, there were 15.9 million children[118] born HIV-free (CBHF) from women living with HIV. CBHF remain more likely to be born small[121], exhibit worse rates of stunting[123], and have poorer neurodevelopment[126] than CHU by 2 years of age. Both universal and HIV-specific risk factors contribute to these differences including maternal HIV and its medication, co-infections, dysbiosis, inflammation, malnutrition and stress[124]. It is plausible that these early-life exposures may have persistent effects long after the antenatal HIV exposure has ended.

Early-life results from CBHF in the SHINE cohort have been previously described in Chapter 1. There are very few studies that have performed long-term follow-up to investigate whether the early-life differences observed in CBHF persist to school age, or simultaneously examined growth, cognitive and physical function. This chapter aims to follow-up a subgroup of CBHF and CHU within the SHINE cohort at age 7 years to evaluate whether there were school-age differences in growth, physical and cognitive function[374]. School-age is highly predictive of later adult size and function: Evaluating whether CBHF catch-up or continue to grow and develop less well has important public health implications for the expanding numbers of CBHF.

6.2 Methods

Statistical analysis

CHU were defined as children born to mothers who tested negative for HIV throughout the pregnancy, and wherever possible an updated status for the mother-child pair was confirmed. Children who were HIV-exposed were categorised as being born to mothers testing positive for HIV during pregnancy[122]. CBHF were specified as children who were HIV-exposed and confirmed HIV-negative by 18 months of age (which was the SHINE trial endpoint)[141].

A pre-specified statistical analysis plan was published online at https://osf.io/8e2zh. Stata v13 and v17 were used for analyses. Baseline characteristics between CHU and CBHF groups were compared using multinomial and ordinal regression models, and Somers' D for medians. Within-cluster correlation was handed with robust variance estimation. Generalised estimating equations (GEE) were used to evaluate any difference between the SAHARAN outcomes for CBHF and CHU groups. Model 1 adjusted for trial factors: exact age of child, sex of child, randomized intervention arm, data collector performing the assessment, and calendar season. Model 2 included these trial factors plus contemporary demographic and socioeconomic confounders derived from a directed acyclic graph (DAG) with online software (Dagitty.net), (see appendix Fig A6-1). These included socioeconomic status[139], household food insecurity assessment scale (HFIAS), adversity score, household religion, caregiver education, caregiver age, caregiver depression (Edinburgh Postnatal Depression Score, EPDS), caregiver social support[140], caregiver gender norms[140], and the number of children's books at home. Model 3 included the trial factors previously described and baseline socioeconomic and demographic confounders also derived from a DAG (see Appendix Fig A6-2): household socioeconomic score, household dietary diversity score, maternal education, maternal haemoglobin, baseline EPDS, maternal gender norms, birthweight and health facility births. A pre-specified subgroup analysis examined evidence for an interaction of CBHF with child sex using a cut-off of $p<0.10$.

6.3 Results

Follow-up of CBHF and CHU

Between 22 November 2012 and 27 March 2015, 5280 pregnant women were enrolled at median 12 (IQR 9, 16) gestational weeks from 211 clusters in Shurugwi and Chirumanzu districts (Appendix Figure A6-3). In Shurugwi, there were 420 births to women living with HIV and 2174 births to women without HIV. Of these, 376 children born HIV-free (CBHF) and 2016 HIV-unexposed children (CHU) completed the 18-month primary endpoint visit. Between 18 months and 7 years, 2 (0.5%) CBHF and 5 (0.2%) CHU died, whilst 6 (1.6%) CBHF and 42 (2.1%) CHU could not be traced and were presumed lost to follow-up. Two caregivers of CBHF and 9 caregivers of CHU declined follow-up when approached for their children to be measured at 7 years. There were 87 (23.2%) relocations among CBHF and 387 (19.2%) relocations among CHU outside of Shurugwi. These relocated children were also excluded. The prevalence of adversity in CBHF households was broadly similar (Table A6-1). Overall, 273 HIV-exposed children were measured, of whom 5 were HIV positive and 4 had severe disability (see Appendix table A6-2). Hence 264 CBHF were included for comparison with CHU. Of 1002 CHU measured, 12 were excluded: 2 were HIV-positive (due to mothers seroconverting during breastfeeding) and 10 had severe disability (see Chapter 3 table 3-6). Therefore 990 CHU were included in the comparison with 264 CBHF.

For mothers living with HIV (MLWH) and recruited into SHINE follow-up (SFU), their baseline characteristics were broadly similar to those MLWH not enrolled (Appendix table A6-3). Enrolled MLWH had a higher inter-quartile range for distance walking to water and a lower average water volume usage. Enrolled MLWH had slightly higher median number of chickens (5 vs 4) and higher rates of livestock observed inside the house. MLWH who were enrolled into SFU were slightly older (30.2 vs 28.6 years) had marginally higher pregnancy MUAC and haemoglobin and lower rates of employment. At 18 months, SFU CBHF had a marginally higher MUAC Z-score compared to those not enrolled (-0.1 vs -0.2) Z-scores. Overall differences for MLWH and CBHF were minimal between those enrolled and not enrolled, so it appeared that MLWH and CBHF were broadly representative of the whole SHINE cohort.

Participant characteristics for CBHF compared with CHU

The contemporary characteristics of the child, caregiver and household at the time of the follow-up visit were compared between CBHF and CHU in Table 6-1. CBHF had a higher proportion of caregivers who were mothers (83.1% vs 75.9%) compared to other types of caregiver such as grandmothers or other family members. CBHF also had a greater proportion of households that had been randomized to the WASH or combined arms. This reflected the fact that all available CBHF in Shurugwi were approached for enrolment into SHINE follow-up without any randomization. CBHF households had markers of increased deprivation compared to CHU households, including higher levels of food insecurity. In the past 28 days as measured by the HFIAS score (12.9 vs 12.0) and also a higher total adversity score (1.95 vs 1.77) compared to CHU households. Caregivers of CBHF versus CHU had slightly fewer mean years of schooling (9.5 vs 10.0), although both were relatively high. CBHF caregivers also had higher Edinburgh postnatal depression scores (EPDS) (4.1 vs 3.2) compared to CHU. For children, CBHF also had lower total schooling exposure (3.1 vs 3.3 years) compared to CHU.

Characteristics	Variable at 7-year visit	CBHF N=264	CHU N=990	p-value
Child	Proportion female [N]	51.1% [135]	51.1% [506]	0.99
	Child age, years; mean (SD)	7.3 (0.3)	7.3 (0.2)	0.07
	Mean years of schooling (SD)	3.1 (0.7)	3.3 (0.8)	0.01
Caregiver	Mother as caregiver, % [N]	83.3% [219]	75.8% [750]	0.01
	Mean years of schooling (SD)	9.5 (2.7)	10.0 (2.6)	0.01
	Mean Edinburgh Postnatal Depression (EPDS) score (SD)	4.0 (4.7)	3.2 (4.4)	0.01
	Mean Social support score (SD)	3.8 (0.6)	3.9 (0.5)	0.38
	Mean Gender norm attitudes (SD)	4.1 (0.6)	4.1 (0.6)	0.62
	Mean Total Discipline score (SD)	2.0 (2.1)	1.9 (2.0)	0.62
	Mean Child parent relationship score (SD)	3.3 (0.8)	3.3 (0.7)	0.21
Household characteristics	SES quintile, % [N]			
	lowest	23.7% [62]	19.1% [186]	0.50
	second	20.3% [53]	19.8% [193]	
	middle	19.2% [50]	20.2% [197]	
	fourth	19.2% [51]	20.2% [197]	
	highest	17.7% [46]	20.6% [201]	
	Mean SES scale (SD)	1.5 (0.7)	1.6 (0.6)	0.06
	Mean Household Food Insecurity Assessment Scale (SD)	12.9 (4.7)	12.0 (4.2)	0.005
	Mean Household Dietary Diversity Scale (SD)	7.7 (2.0)	7.7 (1.8)	0.91
	Mean Total Household Water Insecurity Experiences scale (SD)	12.2 (1.3)	12.1 (0.9)	0.41
	Female headed household, % [N]	18.6% [50]	17.1% [171]	0.56
	Mean Adversity Score (SD)	1.9 (1.5)	1.8 (1.4)	0.07
	Median number of children's books at home (IQR)	0 (0, 1)	0 (0, 1)	0.02
Original trial arm	SOC	19.3% [51]	24.9% [246]	<0.001
	IYCF	17.4% [46]	25.3% [250]	
	WASH	35.2% [93]	25.0% [247]	
	Combined	28.0% [74]	25.0% [247]	

Table 6-1 Contemporary characteristics of CBHF vs CHU.

All variables were measured at the time of the follow-up visit. Baseline factors for CBHF and CHU measured during participation in the original trial are shown in Appendix table A6-3 IQR: inter-quartile range, SES: socioeconomic status.

The baseline characteristics of the mother and household were also compared. These were measured at enrolment to the original trial during pregnancy, together with child characteristics between birth and the 18 months trial endpoint (see Appendix table A6-3). Mothers living with HIV (MLWH) had lower mid-upper arm circumference (MUAC) and haemoglobin, and higher parity than mothers without HIV. MLWH also had higher depression and food insecurity scores, and lower socioeconomic scores. For the children, CBHF had lower breastfeeding duration and smaller anthropometry measurements at 18 months, including reduced length, weight, head circumference and MUAC Z-compared to CHU (see Appendix table A6-4).

Cognitive function of CBHF compared to CHU

Cognitive outcomes for CBHF and CHU were compared in Table 6-2. CBHF had a lower Mental Processing Index from the KABC-II test, which reflected overall cognitive function and suggested globally reduced neurodevelopment. Strong evidence of difference remained after adjustment for contemporary factors using model 2 or baseline factors using model 3. CBHF also had lower scores in literacy and numeracy on the School Achievement Test and reduced executive function as measured by the Plus-EF score. All of these cognitive differences remained with adjusted models. Fine motor function suggested slower finger coordination among CBHF, but there was weaker evidence of difference after adjustment for contemporary or baseline factors. There was no evidence of difference between CBHF and CHU for the Strengths and Difficulties Questionnaire or the child's own socioemotional score. Overall, CBHF showed lower neurodevelopmental scores by 0.2-0.3 standard deviations, across a range of measures of cognition, executive function and academic achievement.

The differences in cognition were also examined in detail by individual subtest (Appendix table A6-5). It was clear that CBHF demonstrated globally reduced scores across all subtests and domains of the KABC-II. Similarly, the school achievement test showed CBHF scored worse for numeracy, reading and writing. For the Plus EF, the Multi-source Interference test and Stars and Flowers executive function tests had strong evidence of difference, but this was weaker for the fish flanker test on adjustment.

Outcome	CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
Cognitive test	N	Mean (SD)	N	Mean (SD)	Unadjusted difference	Adjusted difference Model 1 (Trial factors)	Adjusted difference Model 2 (Trial factors & contemporary covariates)	Adjusted difference Model 3 (Trial factors & baseline covariates)
Mental Processing Index	264	45 (11)	990	48 (11)	3 (2, 4)	3 (2, 4)	3 (1, 4)	3 (2, 4)
School Achievement Test	264	39 (26)	990	46 (28)	7 (4, 11)	7 (3, 11)	6 (2, 10)	6 (3, 10)
Plus EF executive function score	251	109 (25)	978	114 (24)	5 (2, 8)	5 (2, 8)	5 (2, 8)	5 (2, 9)
Fine motor speed, seconds	262	25.0 (6.7)	986	24.1 (6.6)	-1.0 (-1.8, -0.1)	-0.8 (-1.7, 0.1)	-0.8 (-1.7, 0.1)	-0.7 (-1.6, 0.2)
Strengths & Difficulties Questionnaire score	263	9 (5)	989	9 (5)	0 (-1, 0)	-1 (-1, 0)	0 (-1, 1)	0 (-1, 0)
Child socioemotional score	256	4 (1)	973	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Table 6-2 Cognitive function compared between CBHF and CHU.

Model 1 adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling). Overall, 25 Plus-EF measurements were missing due to a programming error on encryption which led to some results being lost. For fine motor assessments, 6 children did not perform the task: 1 child's caregiver refused, and 5 children were unable to fully understand or concentrate for the finger tapping task. Two caregivers did not answer all SDQ questions. Overall, 25 children refused to answer all questions on the child socioemotional scale, hence were unable to provide a full score.

Physical function of CBHF compared to CHU

Physical function scores for both CBHF and CHU were compared in Table 6-3. CBHF generally scored lower for all physical function tests. However, the only test with strong evidence of difference between groups that continued with adjusted models was for the highest level achieved in the shuttle run test. This represented cardiovascular fitness, calculated as VO_2max which was the maximum amount of oxygen an individual can utilise during intense exercise. CBHF compared to CHU had a 0.7 ml kg^{-1} min^{-1} lower VO_2max, representing 0.3 lower average level on the shuttle run test. This was approximately a 60 metres shorter distance run by CBHF before they were too tired.

When further secondary outcomes for physical function were examined (Appendix table A6-6) CBHF again tended to have weaker values of grip strength across both hands, but only cardiovascular fitness had strong evidence of difference across adjusted models. Blood pressure also had marginally lower values for CBHF, but there was little evidence that this continued across adjusted models.

Outcome	CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
Physical function test	N	Mean (SD)	N	Mean (SD)	Unadjusted difference	Adjusted difference Model 1 (Trial factors)	Adjusted difference Model 2 (Trial factors & contemporary covariates)	Adjusted difference Model 3 (Trial factors & baseline covariates)
Grip Strength, Kg	262	10.5 (1.9)	990	10.7 (1.9)	0.2 (-0.1, 0.5)	0.3 (0.0, 0.5)	0.3 (0.0, 0.5)	0.2 (-0.0, 0.5)
Broad jump, cm	259	111.0 (17.3)	987	112.8 (15.1)	2.1 (-0.2, 4.3)	2.5 (0.3, 4.6)	2.1 (-0.2, 4.3)	1.8 (-0.3, 4.0)
VO_2max, ml kg^{-1} min^{-1}	255	50.2 (2.7)	986	50.9 (2.7)	0.8 (0.4, 1.2)	0.6 (0.2, 1.0)	0.5 (0.1, 0.9)	0.5 (0.1, 0.9)
Systolic BP, mm Hg	264	96.7 (9.0)	988	97.0 (9.3)	0.1 (-1.1, 1.2)	0.5 (-0.5, 1.6)	0.6 (-0.4, 1.7)	0.6 (-0.5, 1.6)
Diastolic BP, mm Hg	264	62.8 (7.3)	988	62.3 (7.5)	-0.5 (-1.5, 0.4)	0.0 (-0.9, 1.0)	0.0 (-0.9, 1.0)	0.1 (-0.9, 1.1)

Table 6-3 Physical function compared between CBHF and CHU.

Model 1 is adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 is adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 is adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling). Two children (both CBHF) did not perform the grip strength test: 1 was not motivated and 1 had a caregiver who refused the measurements. Eight children did not perform the broad jump test for a variety of reasons: 1 caregiver refused, 1 visit was performed during heavy rains and the ground was too slippery, 2 children had painful legs, 2 children's caregivers refused due to the child being known to have asthma, 1 child refused and 1 measurement was missing without a recorded reason. In addition, 5 children did not do the shuttle run test: 3 children refused, 1 was recorded as having asthma, and 1 measurement was missing without a recorded reason. Two children refused blood pressure measurements.

Growth and Body composition of CBHF compared to CHU

Growth and body composition for both groups were reflected in Table 6-4 (and appendix table A6-7). CBHF generally had smaller growth and reduced body composition values than CHU. However, the only strong evidence of difference was for head circumference, which was 0.3 cm lower in CBHF, including for adjusted models. Overall, CBHF generally had weaker physical function scores and lower growth, with strong evidence of difference for cardiovascular fitness and head circumference.

Table 6-4 Growth and body composition in CBHF and CHU.

Model 1 is adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 is adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 is adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling). One caregiver refused all anthropometry measurements. Five children refused skinfold measurements, three children had a missing weight due to faulty weighing scales, nine children had missing bioimpedance measurements because of faulty machines or measurements that were excluded for inconsistency, two children refused haemoglobin measurements, and one child had missing knee-heel length, MUAC, waist and calf circumference measurements.

Outcome	CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
Growth and Body Composition	N	Mean (SD)	N	Mean (SD)	Unadjusted difference	Adjusted difference Model 1 (Trial factors)	Adjusted difference Model 2 (Trial factors & contemporary covariates)	Adjusted difference Model 3 (Trial factors & baseline covariates)
Height-for-age Z score	263	-0.6 (0.9)	990	-0.5 (0.9)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)
Weight-for-age Z score	262	-0.7 (0.9)	988	-0.6 (0.9)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)
Body mass index, kg/m^2	262	-0.5 (0.9)	988	-0.5 (0.8)	0.0 (-0.2, 0.1)	0.0 (-0.1, 0.1)	0 .0 (-0.2, 0.1)	0.0 (-0.1, 0.1)
Knee-heel length, cm	262	37.3 (2.0)	989	37.4 (1.9)	0.1 (-0.1, 0.4)	0.2 (0.0, 0.5)	0.2 (-0.1, 0.4)	0.1 (-0.1, 0.4)
Head circumference, cm	263	51.0 (1.5)	990	51.3 (1.4)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)
Mid-upper arm circumference, cm	262	17.0 (1.4)	989	16.9 (1.3)	-0.1 (-0.3, 0.1)	0.0 (-0.2, 0.2)	0 (-0.2, 0.2)	0.0 (-0.2, 0.1)
Waist circumference,	263	54.1 (3.1)	989	54.1 (3.1)	-0.1 (-0.6, 0.3)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	0.0 (-0.4, 0.4)

Outcome	CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
cm								
Hip circumference, cm	263	61.0 (4.1)	990	60.9 (3.9)	-0.1 (-0.7, 0.5)	0.1 (-0.5, 0.7)	0.1 (-0.5, 0.7)	0.0 (-0.6, 0.6)
Calf circumference, cm	263	23.3 (1.6)	989	23.4 (1.7)	0.1 (-0.1, 0.3)	0.2 (0.0, 0.4)	0.2 (0, 0.4)	0.2 (-0.1, 0.4)
Lean mass index, $Ohms^{-1}$	262	12.1 (1.3)	982	12.1 (1.3)	0.0 (-0.2, 0.2)	0.0 (-0.1, 0.2)	0.0 (-0.2, 0.2)	0.0 (-0.1, 0.2)
Impedance Index, $m^2/Ohms^{-1}$	262	1.7 (0.3)	982	1.8 (0.3)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0 .0 (0.0, 0.1)	0.0 (0.0, 0.1)
Phase angle, degrees	261	5.1 (0.5)	982	4.9 (0.6)	-0.1 (-0.2, 0.0)	-0.1 (-0.1, 0.0)	-0.1 (-0.2, 0)	-0.1 (-0.1, 0.0)
Total skinfold thicknesses, mm	261	26.4 (6.0)	987	27.1 (6.2)	0.6 (-0.3, 1.5)	0.7 (-0.2, 1.6)	0.7 (-0.2, 1.6)	0.6 (-0.2, 1.5)
Peripheral skinfold thickness, mm	261	15.7 (3.6)	988	16.2 (3.7)	0.5 (0.0, 1.0)	0.5 (0.0, 1.0)	0.5 (0.0, 1.0)	0.5 (0.0, 1.0)
Central skinfold thickness, mm	263	10.9 (3.1)	989	10.9 (3.1)	0.1 (-0.4, 0.5)	0.1 (-0.3, 0.6)	0.1 (-0.4, 0.7)	0.1 (-0.4, 0.6)
Haemoglobin, $g\ dl^{-1}$	261	12.6 (1.3)	990	12.7 (1.2)	0.0 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.2)

The impact of child sex on CBHF compared to CHU

A pre-specified subgroup analysis examined the interaction of child sex on CBHF compared to CHU (Appendix Table A6-8). For cognitive outcomes, there was evidence of an interaction between child sex and the Strengths and Difficulties questionnaire: among boys, CHU scored better than CBHF (1 mark, 95% CI 0, 2) but among girls, there was no evidence of difference in SDQ score between CBHF and CHU. The difference between CBHF and CHU for both sexes was negligible for the child socioemotional score (0 marks, 95% CI 0, 0).

Among physical function outcomes, there was evidence of an interaction between child sex and VO_2max. CHU boys had better cardiovascular fitness than CBHF boys (1.2, 95% CI 0.6, 1.8), while there was no evidence of difference between groups among girls. For growth outcomes, there was evidence of an interaction between sex and calf circumference such that CHU girls had weak evidence for a slightly larger calf circumference (0.3 cm, 95% CI 0.0, 0.6) than CBHF girls. There was no evidence of a difference in calf circumference for boys between CBHF and CHU. There was no evidence of interactions with child sex for other growth or body composition outcomes.

6.4 Discussion

As the population of children born HIV-free continues to expand, it was observed that despite ART during pregnancy, CBHF in sub-Saharan Africa have poorer early-life growth[123] and neurodevelopment[375]. However, it was unclear whether disparities widen, persist, or resolve over time. The SHINE Follow-up study has demonstrated evidence for persistently reduced cognitive and physical function among CBHF at 7 years of age. Potential biological and environmental mechanisms for these disparities in CBHF are discussed below. A substantial gap in neurodevelopment was observed, and may have increased when compared to the disparity in neurodevelopmental scores at age 2 years in the SHINE cohort[122]. CBHF also had lower shuttle run scores illustrating reduced cardiovascular fitness. This may signify worse adult health and function. Overall, this chapter has highlighted the ongoing modest reductions in cognitive and physical function for CBHF, which are still detectable many years after exposure to HIV *in utero*. This may have a substantial long-term impact on human capital for areas of high HIV prevalence. It is important to understand the underlying drivers of these differences, to deploy appropriate interventions to improve the long-term outcomes in the growing population of CBHF.

Multiple domains of cognitive function were affected for CBHF including cognitive processing, academic and executive function. The tools used had been previously adapted[238] and piloted for children at this age and in this setting[192]. There was a 0.3 standard deviation reduction in the Mental Processing Index for CBHF (representing the overall cognitive processing score) when compared to CHU. CBHF also demonstrated lower school achievement test scores and executive function scores. This global effect across a range of cognitive domains had been previously shown in early life[126]. In a meta-analysis of 11 studies (6 outside the USA) of relatively small sample sizes, CBHF showed reduced neurodevelopment compared to CHU at young ages [375]. More recent studies have shown increased risk of language delay in CBHF[376,377], but the majority of CBHF studies have measured children below 2 years of age. The SHINE Follow-up study has shown that effects of HIV-exposure persist across cognitive domains up to the age of 7 years. Exploratory analysis showed these reductions occurred globally across all the subtests of these assessments. The only exception was in the Flanker test in the executive function test battery, which had a weak evidence of difference (Appendix Table A6-5).

CBHF have previously been noted to have a smaller head circumference in early life [378], which was also observed in SHINE Follow-up. Poorer neurodevelopmental outcomes have also been strongly associated with reduced postnatal head circumference at age 2 years [379]. Beyond gross measures of brain size, more detailed evidence of structural differences among CBHF has emerged recently, with a reduction in grey matter volume observed as early as

3 weeks of age using MRI[125], as well as diffuse tensor imaging combined with neuropsychological testing[380]. Head circumference is predominantly viewed as a marker of growth in the first 2 years[381]. Despite catch-up in other anthropometric measures over time seen in SFU, the signal of reduced head growth persisted to school-age, suggesting a long-term impact on brain structure. This was consistent with the accompanying reductions in neurodevelopment.

Both HIV-specific and universal risk factors contribute to cognitive disparities for CBHF[124]. Regarding environmental factors, the psychosocial and socioeconomic environment was more challenging for CBHF in SHINE Follow-up, with worse scores seen in food security, adversity, caregiver depression and fewer years of schooling reported for caregivers. Combined with the slightly reduced child schooling exposure in CBHF, all of these factors could interact and affect the way caregivers provide nurturing care and how CBHF develop. However, adjusted models that included either contemporary or baseline psychosocial variables did not remove the observed reductions in cognitive function for CBHF, although the disparity was reduced. Differences in growth and function that were still detectable at 7 years may also be driven by biological factors such as antenatal HIV, ART exposure, co-infections, and greater inflammation[374]. It is likely that a combined intervention approach that tackles both universal and HIV-specific pathways would be needed to reduce the cognitive gap for CBHF. This would likely need to be delivered for longer than the SHINE interventions, starting in early life and including school-age.

CBHF also showed a reduction in the level obtained in the shuttle run, reflecting a lower VO_2max and hence lower cardiovascular fitness than CHU. There could be several mechanisms behind this: HIV exposure may have effects on cardiac structure and function, as observed in high-income CBHF cohorts[382,383]. ART exposure may also impair myocardial growth in the fetus[383]. For example, Zidovudine has been shown to cause mild antenatal dysfunction and fetal cardiac remodelling[384]. HIV itself may also have an effect: In a large study of 400 American CBHF, higher cardiac inflammation and left ventricular stress were found in children living with HIV than those perinatally exposed to HIV, but it is feasible that any HIV exposure may also cause long-lasting cardiac changes[385]. A separate case-control study in 30 school-age American CBHF compared to CHU showed a 0.5 standard deviation reduction in the left ventricular mass index[386]. A subgroup analysis by sex of CBHF in SHINE follow-up (SFU) demonstrated that the reduction in cardiovascular fitness was observed in boys only. However, previous cardiac remodelling in the USA has been noted to be more pronounced in girls[382]. Therefore, an alternative explanation for the sex difference observed in SFU may be differences in lung function between groups. It was previously observed that CBHF have increased mortality from respiratory infections[124], and these infections may also cause long-term morbidity in lung function. In South Africa, CBHF showed negative associations between lung function and delays in starting ART, low maternal CD4 count and high viral loads[387]. Therefore, further detailed measurements of both cardiac and lung physiology would be needed in CBHF cohorts to better understand the reasons for the reduced cardiovascular fitness observed in mid-childhood in SFU. The weak evidence for reduced calf circumference in CBHF girls was not associated with any concomitant reductions in physical function for CBHF girls.

The long-term comparison within the SHINE follow-up study of CBHF to CHU had several strengths, particularly the use of an extensively piloted toolbox[192] with suitably adapted cognitive assessments[237]. The simultaneous characterisation of multiple measures of growth, physical and cognitive function also provided greater detail than previously available. The SHINE cohort had well-characterised longitudinal HIV exposure status, and measured baseline and contemporary maternal, socioeconomic and nurturing factors. This enabled adjusted models to be constructed with detailed covariates. The SHINE Follow-up (SFU) substudy was also likely to be representative of the broader SHINE cohort given no significant differences were observed between those included and excluded in the SFU.

There were also several study limitations. Firstly there was potential survivor bias due to higher mortality previously observed in this cohort in CBHF[388]. Selection bias was also a concern due to the high number of relocations since the end of the trial, which may have been related to greater household socioeconomic insecurity. Further detailed information was also needed for the mothers' HIV treatment. It was not possible to evaluate the impact of specific antiretroviral regimens on long-term child health outcomes. Finally, this was an exploratory analysis with many correlated outcomes with a lack of adjustment for multiple comparisons. However, the consistent findings across multiple cognitive tests provides some reassurance that the differences observed for CBHF were unlikely to be wholly from inflated type 1 error.

In conclusion, the measurement of CBHF in SHINE follow-up and their comparison with CHU provided one of the few birth cohorts in sub-Saharan Africa to be followed up to school-age. Ongoing vulnerabilities among CBHF were demonstrated in multiple domains of cognitive function, cardiovascular fitness and head circumference. This could have long-term implications for the health and human capital of CBHF across the life-course. A clear objective for the future would be to understand the relative contributions of biological and psychosocial factors that generated these long-term disparities. This would inform future interventions that may include nurturing care and educational provision for children, combined with psychosocial support and nurturing care for caregivers[374]. Given the expanding global population of CBHF, further characterisation and long-term follow-up studies across the life-course are urgently needed.

7 The impact of the SHINE early-life interventions

7.1 Introduction

Hypotheses tested

Chapter 7 aims to determine what impact the SHINE early-life interventions had on school-age child growth, cognitive and physical function for children born to mothers without HIV (CHU, or alternatively defined as children unexposed to HIV). The main hypothesis tested was that the improved infant and young child feeding (IYCF) intervention increased cognitive function of children at age 7 years, as measured by the mental processing index (MPI), which was the total of the Kaufman Assessment Battery for Children (KABC-II). Secondary hypotheses tested were that IYCF also impacted other cognitive and physical function outcomes, as well as growth and body composition.

Another secondary hypothesis tested was that the SHINE Water, Sanitation and Hygiene (WASH) interventions had no effect, given they had no discernible impact in early life. This chapter initially describes the importance of follow-up of the SHINE cohort.

The importance of follow-up of the SHINE trial

The SHINE Trial was previously described in chapter 1[73]. For children born to mothers without HIV, results at 18 months showed that IYCF improved HAZ at age 18 months by 0.16 (95%CI 0.08, 0.23) Z-scores. IYCF also decreased stunting by 21%, while WASH had no effect on growth[73]. IYCF similarly improved child haemoglobin by 2.03 g/L (95%CI 1.28, 2.79), whilst again WASH had no discernible impact[73]. In a sub-study at 2 years of age, there was no significant impact on child neurodevelopment of either SHINE IYCF or WASH interventions[77].

The SHINE cohort provided a unique opportunity to characterise the long-term effects of early-life IYCF and WASH interventions built on the foundation of a birth cohort with a successful breastfeeding intervention across all arms[135]. The SHINE study was located within a rural population with a high prevalence of stunting and adversities, that was broadly applicable to faltering growth within Sub-Saharan Africa.

7.2 Methods

SHINE Follow-up

To evaluate the long-term effects of IYCF and WASH on child health outcomes within the SHINE study, the SAHARAN toolbox was applied to measure child growth, body composition, physical and cognitive function at 7 years of age[192] as described in chapter 3. 250 children born to HIV-negative mothers per intervention arm were randomly selected from the SHINE database. Children who were unable to be visited for various reasons or whose caregiver declined participation were randomly replaced with another eligible SHINE child from the same trial arm. Details of the SHINE follow-up (SFU) study have been previously described in chapter 3[12]. A pre-specified statistical analysis plan (SAP) for the follow-up study were registered at https://osf.io/8e2zh.

Statistical analysis

The study team remained blinded to the child's original SHINE intervention arm until all data were collected and cleaned. Unblinding then occurred with pre-written and pre-tested code. Stata (version 15 and 17) was used for all analyses. Baseline characteristics of the participants enrolled in the SFU study were compared between trial arms while handling within-cluster correlation using multinomial regression models with robust variance estimation. Analyses were intention-to-treat for all the SAHARAN toolbox outcomes at the child level. The study arm was defined as the mother's residence at the time of consent into the original SHINE trial. The SAHARAN toolbox[192] outcomes were all continuous measures with normal distributions. Hence the absolute difference in mean score between treatment groups was estimated using generalised estimating equations with an exchangeable working correlation structure. This accounted for within-cluster correlation.

The SHINE Follow-up (SFU) study was not powered to detect a statistical interaction between the IYCF and WASH interventions. However, a statistical interaction was estimated for one key outcome within each domain of cognition, physical function and growth. For cognition it was the MPI, for physical function it was grip strength and for growth it was HAZ. If the interaction term was observed to be significant ($p<0.05$ from a Wald test), or there was a sizeable point estimate (difference in mean score >0.25 standard deviations), then a regression model with three dummy variables was used for all outcomes in that domain compared to the SOC. Each dummy variable represented the comparison of the standard of care (SOC) arm to each of the three treatment arms (IYCF, WASH and IYCF + WASH). If the interaction term was not significant, then a regression model with two terms was applied to represent the combined treatment arms. For example, the effects of IYCF were then estimated by combining the two IYCF arms (IYCF and IYCF+WASH) and comparing them with the two non-IYCF (WASH and SOC) arms. Similarly, the effects of WASH were then estimated by combining the two WASH arms (WASH and IYCF+WASH), and comparing them with the two non-WASH arms (IYCF and SOC). The primary analysis was unadjusted.

Adjusted analyses included prespecified baseline covariates as specified in the SAP. These included trial factors such as calendar date of measurement, child sex, study nurse, average ambient temperature during the assessment, and exact age. Additional baseline covariates were selected based on a directed acyclic graph designed whilst still blinded.

Interactions of SAHARAN toolbox outcomes with child sex were explored, as stated in a pre-specified sensitivity analysis. If $p < 0.10$ for any outcome, separate GEE models for boys and girls were used (see Appendix table

A7-3). A post-hoc exploratory analysis examined SHINE intervention effects split by children with or without stunting at 18 months. As previously stated in Chapter 1, for the primary outcome of IYCF effect on MPI, 1000 children (500 IYCF vs 500 non-IYCF assuming no interaction between interventions), provided 86% power to detect a 0.2 standardised effect size in the absolute MPI difference between intervention and control arms. This assumed an intra-cluster correlation of 0.05 and sampling from 100 clusters, with alpha of 0.05. By capitalising on SHINE's 2x2 factorial design, a similar sensitivity was available for the secondary outcome of WASH (i.e 500 WASH vs 500 non-WASH).

7.3 Results

SFU comparison between arms

A comparison of the baseline characteristics of the children enrolled into SFU with the rest of the SHINE cohort has already been described (Chapter 4). When comparing between intervention arms, baseline characteristics (measured at enrolment to SHINE during pregnancy), were broadly similar for those re-enrolled into SFU (Appendix Table A7-1). Children in the WASH and SOC arms in the SHINE Follow-up substudy had a higher prevalence of stunting and lower height-for-age and weight-for-age Z-scores at 18 months, reflecting the impact of the SHINE interventions[73] Appendix Table A7-2).

Development of the adjusted model

The effect of the SHINE interventions on school-age growth, cognitive and physical function was adjusted by baseline covariates. For the adjusted model, a Directed Acyclic Graph was constructed before unblinding by considering baseline environmental, maternal and nurturing factors:

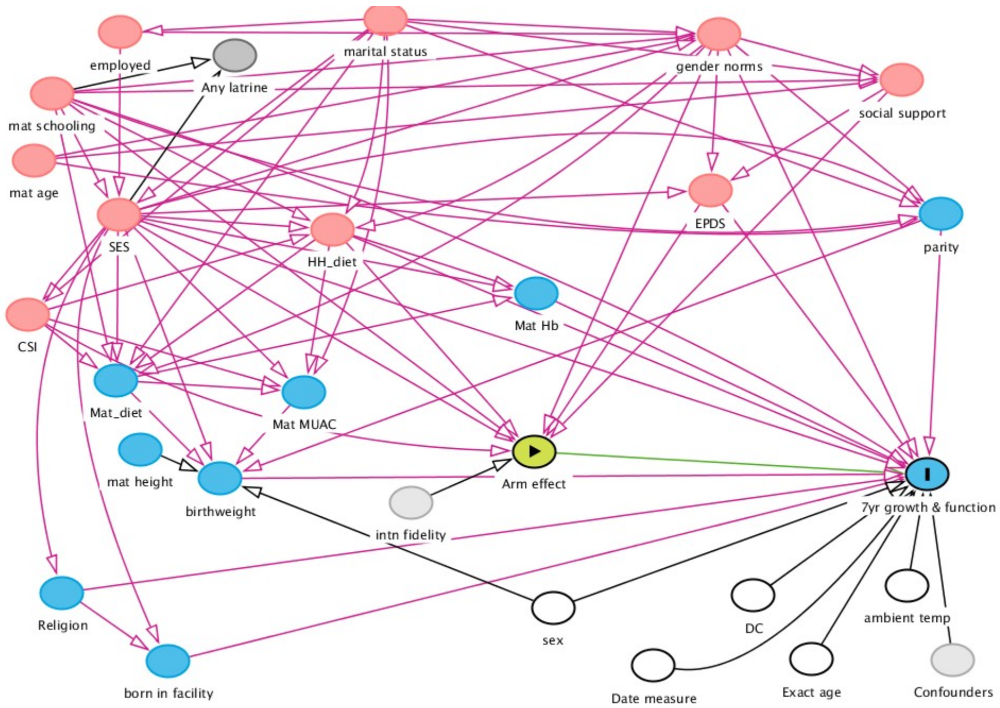


Figure 7-1 DAG exploring SHINE intervention effects on SAHARAN outcomes

Directed acyclic graph (DAG) exploring the effect of covariates in the relationship between SHINE interventions and school-age growth, cognitive and physical function. Environmental covariates were grouped at the top left, with maternal and nurturing on the right side and trial factors at the bottom right. CSI: Coping strategies index, SES: wealth index score, mat age: maternal age, mat schooling: maternal schooling in years, HH_diet: household dietary diversity score, EPDS: Edinburgh Postnatal Depression Score ,employed: if mother employed, marital status, gender norms score, social support score, Mat Hb: Maternal haemoglobin, mat_diet: Maternal dietary diversity score, Mat MUAC: maternal MUAC score. Intervention fidelity and other confounders were not measured in this DAG.

Directed acyclic graphs (DAGs) were used to identify the confounding variables that were required within adjusted models for the effect of the SHINE intervention on SAHARAN outcomes. Hence the DAG was drawn on Dagitty and the variables for adjustment were identified before examining the data in detail. The adjusted model therefore included the following covariates: child age, sex, study nurse, calendar date measured, ambient temperature, age, ambient temperature, baseline depression score (EPDS), household dietary diversity score, maternal dietary diversity score, wealth index, birthweight, gender norms score, maternal education and parity.

Effect of SHINE interventions on cognitive function outcomes

Table 7-1 Effect of SHINE early-life IYCF and WASH interventions on cognitive outcomes.

IYCF: Infant and Young Child Feeding, WASH: Water, Sanitation and Hygiene. Adjusted models included study nurse**,** date measured, exact age of child, ambient temperature, sex of child, maternal depression score (Edinburgh Postnatal Depression Score), household dietary score, maternal dietary score, socioeconomic status as measured by wealth index, birthweight, maternal gender norms, maternal schooling in years, and parity.

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Combined Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	Number in adjusted model	Adjusted diff (95%CI)	p
Mental Processing Index (MPI)	SoC	246	49.2 (12.2)	No IYCF	493	48.8 (11.7)	0.0 (ref)			0.0 (ref)	
	IYCF	250	48.0 (10.4)	IYCF	497	47.8 (10.9)	-0.77 (-2.36, 0.82)	0.344	980	-0.94 (-2.51, 0.63)	0.243
	WASH	247	48.3 (11.1)	No WASH	496	48.6 (11.3)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	47.6 (11.5)	WASH	494	47.9 (11.3)	-0.96 (-2.55, 0.64)	0.239	980	-0.81 (-2.43, 0.81)	0.327
School Achievement Test (SAT)	SoC	246	47.5 (28.5)	No IYCF	493	47.2 (28.2)	0.0 (ref)			0.0 (ref)	
	IYCF	250	46.0 (27.9)	IYCF	497	44.3 (27.4)	-1.74 (-6.42, 2.94)	0.467	980	-1.43 (-5.82, 2.96)	0.524
	WASH	247	46.9 (27.9)	No WASH	496	46.8 (28.2)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	42.5 (26.9)	WASH	494	44.7 (27.4)	-2.34 (-7.02, 2.34)	0.327	980	-1.98 (-6.35, 2.39)	0.375

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Combined Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	Number in adjusted model	Adjusted diff (95%CI)	p
Plus EF Executive function tablet-based test (Plus EF)	SoC	240	114.9 (23.7)	No IYCF	486	113.7 (23.9)	0.0 (ref)			0.0 (ref)	
	IYCF	248	116.0 (23.4)	IYCF	492	115.1 (24.4)	1.49 (-1.75, 4.73)	0.366	968	1.61 (-1.51, 4.73)	0.313
	WASH	246	112.5 (24.2)	No WASH	488	115.5 (23.5)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	244	114.3 (25.4)	WASH	490	113.4 (24.8)	-2.16 (-5.40, 1.08)	0.192	968	-2.22 (-5.41, 0.97)	0.172
Finger tapping coordination (Fine motor, seconds)	SoC	244	23.8 (6.5)	No IYCF	491	23.7 (6.2)	0.0 (ref)			0.0 (ref)	
	IYCF	250	24.7 (7.1)	IYCF	495	24.5 (7.0)	0.74 (-0.12, 1.60)	0.091	976	0.73 (-0.11, 1.56)	0.09
	WASH	247	23.6 (6.0)	No WASH	494	24.2 (6.8)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	245	24.2 (6.8)	WASH	492	23.9 (6.4)	-0.36 (-1.22, 0.50)	0.415	976	-0.63 (-1.51, 0.25)	0.161
Caregiver's score of child's Strengths and Difficulties Questionnaire (SDQ)	SoC	245	9.6 (5.3)	No IYCF	492	9.0 (5.3)	0.0 (ref)			0.0 (ref)	
	IYCF	250	8.6 (5.0)	IYCF	497	8.3 (5.0)	-0.70 (-1.46, 0.05)	0.067	979	-0.67 (-1.41, 0.07)	0.076
	WASH	247	8.4 (5.3)	No WASH	495	9.1 (5.1)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	8.0 (5.0)	WASH	494	8.2 (5.2)	-0.98 (-1.73, -0.22)	0.011	979	-0.96 (-1.72, -0.21)	0.013
Child's socioemotional score from direct interview (Child SocioEm)	SoC	242	3.7 (0.7)	No IYCF	485	3.7 (0.7)	0.0 (ref)			0.0 (ref)	
	IYCF	247	3.7 (0.7)	IYCF	488	3.7 (0.7)	0.03 (-0.04, 0.10)	0.420	963	-0.04 (-0.09, 0.01)	0.161
	WASH	243	3.6 (0.8)	No WASH	489	3.7 (0.7)	0.0 (ref)			0.0 (ref)	

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Combined Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	Number in adjusted model	Adjusted diff (95%CI)	p
	WASH & IYCF	241	3.7 (0.7)	WASH	484	3.7 (0.7)	-0.03 (-0.10, 0.04)	0.400	963	-0.05 (-0.12, 0.01)	0.116

There was no evidence of an interaction between IYCF and WASH for the primary outcome of mental processing index. Therefore, for all cognitive outcomes, intervention effects were assessed by combining the two IYCF-containing arms (IYCF and IYCF + WASH) against non-IYCF (WASH and SOC). Similarly, the two WASH-containing arms were also combined (WASH and IYCF+ WASH) and compared to non-WASH arms (IYCF and SOC).

Examining table 7-1, there was no significant effect of IYCF or WASH on the mental processing index or evidence of an effect on other secondary cognitive outcomes. The primary analysis was unadjusted. The only exception was for a minor improvement in the SDQ score (representing child socioemotional function) in the WASH intervention arms (-0.98 points, 95% CI -1.73, -0.22, p=0.011). This minor improvement also remained in the adjusted analysis.

Effect of SHINE interventions on physical function outcomes

There was evidence of an interaction between IYCF and WASH for the outcome of handgrip strength (p = 0.089), hence all physical function results were analysed by individual trial arm. Examining table 7-2, IYCF led to increased handgrip strength (0.28 Kg, 95%CI 0.02, 0.53, p=0.032), compared to standard-of-care, with weaker evidence in adjusted analysis. In adjusted analyses only, children in the WASH arm had lower diastolic pressure (-1.75 mm Hg, 95% CI -2.86, -0.65, p=0.002) and systolic blood pressure (-1.50 mm Hg 95% CI -2.67, -0.33) compared to children in the standard-of-care arm. The primary analysis was unadjusted.

Table 7-2: Effect of SHINE early-life IYCF and WASH interventions on physical function outcomes.

Table 7-2 Effect of SHINE early-life IYCF and WASH interventions on physical function outcomes.

IYCF: Infant and Young Child Feeding, WASH: Water, Sanitation and Hygiene. Adjusted models included study nurse**,** date measured**,** exact age of child, ambient temperature, sex of child, maternal depression score (Edinburgh Postnatal Depression Score), household dietary score, maternal dietary score, socioeconomic status as measured by wealth index, birthweight, maternal gender norms, maternal schooling in years, and parity.

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
Grip strength, kg	SoC	246	10.6 (1.8)	0.0 (ref)			0.0 (ref)	
	IYCF	250	10.8 (2.0)	0.28 (0.02, 0.53)	0.032		0.22 (-0.01, 0.45)	0.056
	WASH	247	10.7 (2.0)	0.13 (-0.19, 0.44)	0.421	980	0.04 (-0.28, 0.36)	0.8
	WASH & IYCF	247	10.6 (1.9)	0.05 (-0.23, 0.33)	0.734		0.06 (-0.17, 0.29)	0.616
Broad jump, cm	SoC	245	112.8 (15.0)	0.0 (ref)			0.0 (ref)	
	IYCF	249	112.2 (16.4)	-0.60 (-3.45, 2.26)	0.683		-0.92 (-3.69, 1.86)	0.517
	WASH	246	113.0 (14.1)	0.14 (-2.70, 2.98)	0.922	977	0.01 (-2.88, 2.91)	0.993
	WASH & IYCF	247	113.0 (15.0)	0.19 (-2.74, 3.13)	0.899		-0.24 (-3.24, 2.76)	0.875
VO2 max (Shuttle run test), ml/Kg/min	SoC	245	51.1 (2.7)	0.0 (ref)			0.0 (ref)	
	IYCF	248	50.8 (2.5)	-0.37 (-0.91, 0.17)	0.183		-0.43 (-0.94, 0.09)	0.104

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
	WASH	247	50.6 (3.0)	-0.49 (-1.07, 0.09)	0.098	975	-0.26 (-0.84, 0.32)	0.38
	WASH & IYCF	246	50.9 (2.6)	-0.14 (-0.64, 0.36)	0.575		-0.08 (-0.58, 0.42)	0.758
Resting Diastolic blood pressure (BP), mm Hg	SoC	245	62.4 (7.5)	0.0 (ref)			0.0 (ref)	
	IYCF	250	62.4 (7.8)	-0.20 (-1.27, 0.88)	0.717		-0.26 (-1.16, 0.63)	0.563
	WASH	246	61.7 (7.1)	-0.85 (-1.92, 0.21)	0.115	978	-1.75 (-2.86, -0.65)	0.002
	WASH & IYCF	247	62.8 (7.6)	0.54 (-0.65, 1.72)	0.374		-0.1 (-1, 0.8)	0.826
Resting Systolic blood pressure (BP), mm Hg	SoC	245	97.1 (9.2)	0.0 (ref)			0.0 (ref)	
	IYCF	250	96.8 (9.1)	-0.42 (-2.01, 1.16)	0.599		-0.36 (-1.65, 0.93)	0.584
	WASH	246	96.4 (9.0)	-0.78 (-2.10, 0.55)	0.252	978	-1.50 (-2.67, -0.33)	0.012
	WASH & IYCF	247	97.7 (9.8)	0.53 (-1.01, 2.07)	0.503		-0.17 (-1.7, 1.37)	0.829

Effect of SHINE interventions on growth outcomes

There was no evidence of an interaction between the IYCF and WASH interventions on height-for-age Z-score (HAZ). Therefore, for all growth and body composition outcomes, the effects of the SHINE interventions were evaluated by combining the two IYCF-containing arms (IYCF and IYCF+WASH), and comparing them against the non-IYCF arms (WASH and SOC). Similarly the two WASH-containing arms were combined and compared against the non-WASH arms. Examining the effect of the SHINE interventions on school-age growth and body composition (Table 7-3) showed there were no significant effects of the IYCF or WASH interventions on any growth or body composition measures at age 7 years. The primary analysis was unadjusted.

Table 7-3 Effect of SHINE early-life IYCF and WASH interventions on growth and body composition outcomes.

Table 7-3 Effect of SHINE early-life IYCF and WASH interventions on physical function outcomes.

IYCF: Infant and Young Child Feeding, WASH: Water, Sanitation and Hygiene. Adjusted models included study nurse**,** date measured**,** exact age of child, ambient temperature, sex of child, maternal depression score (Edinburgh Postnatal Depression Score), household dietary score, maternal dietary score, socioeconomic status as measured by wealth index, birthweight, maternal gender norms, maternal schooling in years, and parity

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Treatment group	N	Mean S(D)	Unadjusted diff (95% CI)	p	N adj	Adjusted diff (95%CI)	p
HAZ	SoC	246	-0.6 (0.8)	No IYCF	493	-0.5 (0.8)	0.0 (ref)			0.0 (ref)	
	IYCF	250	-0.4 (0.9)	IYCF	497	-0.5 (0.9)	0.09 (-0.01, 0.18)	0.093	980	0.06 (-0.04, 0.16)	0.226
	WASH	247	-0.5 (0.8)	No WASH	496	-0.5 (0.9)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	-0.5 (0.9)	WASH	494	-0.5 (0.9)	0.02 (-0.08, 0.12)	0.711	980	0.02 (-0.08, 0.12)	0.759
WAZ	SoC	245	-0.7 (0.9)	No IYCF	492	-0.7 (0.9)	0.0 (ref)			0.0 (ref)	
	IYCF	249	-0.6 (0.9)	IYCF	496	-0.6 (0.8)	0.04 (-0.06, 0.14)	0.447	978	0.02 (-0.08, 0.12)	0.683
	WASH	247	-0.6 (0.9)	No WASH	494	-0.6 (0.9)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	-0.7 (0.8)	WASH	494	-0.6 (0.8)	0.01 (-0.10, 0.11)	0.898	978	0.00 (-0.11, 0.10)	0.979
BMIZ	SoC	245	-0.5 (0.9)	No IYCF	492	-0.5 (0.9)	0.0 (ref)			0.0 (ref)	
	IYCF	249	-0.5 (0.8)	IYCF	496	-0.5 (0.8)	-0.04	0.538	978	-0.04	0.490

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Treatment group	N	Mean S(D)	Unadjusted diff (95% CI)	p	N adj	Adjusted diff (95%CI)	p
							(-0.16, 0.08)			(-0.16, 0.08)	
	WASH	247	-0.5 (0.9)	No WASH	494	-0.5 (0.8)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	-0.6 (0.8)	WASH	494	-0.5 (0.9)	-0.04 (-0.16, 0.08)	0.541	978	-0.05 (-0.18, 0.08)	0.425
Knee-heel length, cm	SoC	246	37.2 (1.9)	No IYCF	492	37.3 (1.9)	0.0 (ref)			0.0 (ref)	
	IYCF	250	37.6 (1.9)	IYCF	497	37.5 (2.0)	0.16 (-0.06, 0.37)	0.152	979	0.14 (-0.07, 0.34)	0.194
	WASH	246	37.4 (1.9)	No WASH	496	37.4 (1.9)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	37.4 (2.0)	WASH	493	37.4 (1.9)	0.05 (-0.17, 0.27)	0.655	979	0.03 (-0.19, 0.24)	0.797
Head circ, cm	SoC	246	51.3 (1.4)	No IYCF	493	51.2 (1.4)	0.0 (ref)			0.0 (ref)	
	IYCF	250	51.4 (1.5)	IYCF	497	51.4 (1.4)	0.11 (-0.03, 0.26)	0.122	980	0.05 (-0.08, 0.17)	0.451
	WASH	247	51.2 (1.5)	No WASH	496	51.3 (1.4)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	51.4 (1.3)	WASH	494	51.3 (1.4)	-0.01 (-0.16, 0.13)	0.843	980	0.09 (-0.06, 0.24)	0.231
MUAC, cm	SoC	246	16.8 (1.3)	No IYCF	493	16.9 (1.3)	0.0 (ref)			0.0 (ref)	
	IYCF	249	17.0 (1.3)	IYCF	496	17.0 (1.3)	0.10 (-0.08, 0.28)	0.288	979	0.08 (-0.09, 0.26)	0.343
	WASH	247	16.9 (1.3)	No WASH	495	16.9 (1.3)	0.0 (ref)			0.0 (ref)	

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Treatment group	N	Mean S(D)	Unadjusted diff (95% CI)	p	N adj	Adjusted diff (95%CI)	p
	WASH & IYCF	247	16.9 (1.3)	WASH	494	16.9 (1.3)	0.01 (-0.17, 0.19)	0.926	979	-0.05 (-0.22, 0.12)	0.576
Waist circ, cm	SoC	246	54.0 (3.1)	No IYCF	493	54.1 (3.2)	0.0 (ref)			0.0 (ref)	
	IYCF	249	54.2 (3.1)	IYCF	496	54.1 (3.0)	-0.01 (-0.41, 0.39)	0.957	979	-0.04 (-0.44, 0.36)	0.838
	WASH	247	54.1 (3.4)	No WASH	495	54.1 (3.1)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	53.9 (2.9)	WASH	494	54.0 (3.2)	-0.09 (-0.49, 0.30)	0.643	979	-0.12 (-0.55, 0.31)	0.59
Hip circ, cm	SoC	246	60.7 (3.8)	No IYCF	493	60.8 (4)	0.0 (ref)			0.0 (ref)	
	IYCF	250	61.2 (3.9)	IYCF	497	60.9 (3.9)	0.08 (-0.46, 0.63)	0.765	980	0.06 (-0.45, 0.57)	0.818
	WASH	247	61.0 (4.1)	No WASH	496	60.9 (3.9)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	60.7 (3.8)	WASH	494	60.8 (4.0)	-0.13 (-0.67, 0.42)	0.652	980	-0.21 (-0.76, 0.34)	0.455
Calf circ, cm	SoC	245	23.3 (1.7)	No IYCF	492	23.4 (1.7)	0.0 (ref)			0.0 (ref)	
	IYCF	250	23.5 (1.7)	IYCF	497	23.5 (1.6)	0.11 (-0.10, 0.33)	0.299	979	0.08 (-0.12, 0.28)	0.418
	WASH	247	23.4 (1.7)	No WASH	495	23.4 (1.7)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	23.4 (1.6)	WASH	494	23.4 (1.7)	0.01 (-0.20, 0.23)	0.907	979	-0.07 (-0.28, 0.15)	0.541
LMI,	SoC	243	12.0 (1.3)	No IYCF	488	12.1 (1.4)	0.0 (ref)			0.0 (ref)	

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Treatment group	N	Mean S(D)	Unadjusted diff (95% CI)	p	N adj	Adjusted diff (95%CI)	p
Ohms^{-1}	IYCF	248	12.1 (1.3)	IYCF	494	12.2 (1.2)	0.09 (-0.08, 0.26)	0.310	972	-0.04 (-0.18, 0.1)	0.608
	WASH	245	12.1 (1.4)	No WASH	491	12.1 (1.3)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	246	12.2 (1.2)	WASH	491	12.2 (1.3)	0.08 (-0.09, 0.25)	0.360	972	0.07 (-0.07, 0.22)	0.327
I Imp Index M^2 Ohms^{-1}	SoC	243	1.7 (0.3)	No IYCF	488	1.7 (0.3)	0.0 (ref)			0.0 (ref)	
	IYCF	248	1.8 (0.3)	IYCF	494	1.8 (0.2)	0.02 (-0.01, 0.05)	0.138	972	0.00 (-0.02, 0.03)	0.834
	WASH	245	1.8 (0.3)	No WASH	491	1.7 (0.3)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	246	1.8 (0.2)	WASH	491	1.8 (0.3)	0.02 (-0.01, 0.05)	0.262	972	0.02 (-0.01, 0.04)	0.238
Phase Angle, ^{0}	SoC	243	5.0 (0.6)	No IYCF	489	4.9 (0.6)	0.0 (ref)			0.0 (ref)	
	IYCF	247	4.9 (0.6)	IYCF	493	4.9 (0.5)	0.00 (-0.07, 0.07)	0.906	972	0.01 (-0.06, 0.08)	0.812
	WASH	246	4.9 (0.5)	No WASH	490	5.0 (0.6)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	246	4.9 (0.5)	WASH	492	4.9 (0.5)	-0.03 (-0.10, 0.04)	0.418	972	-0.04 (-0.1, 0.02)	0.172
Total skinfold thickness, mm	SoC	245	26.8 (6.1)	No IYCF	492	27.1 (6.4)	0.0 (ref)			0.0 (ref)	
	IYCF	249	27.4 (5.8)	IYCF	495	27.0 (5.9)	-0.02 (-0.86, 0.82)	0.963	978	0.00 (-0.77, 0.78)	0.997
	WASH	247	27.3 (6.8)	No WASH	494	27.1 (5.9)	0.0 (ref)			0.0 (ref)	

Outcome	Effects by arm: Treatment group	N	Mean (SD)	Treatment group	N	Mean S(D)	Unadjusted diff (95% CI)	p	N adj	Adjusted diff (95%CI)	p
	WASH & IYCF	246	26.6 (6.1)	WASH	493	27.0 (6.4)	-0.19 (-1.03, 0.66)	0.666	978	-0.45 (-1.23, 0.32)	0.254
Peripheral skinfold thickness, mm	SoC	245	16.1 (3.7)	No IYCF	492	16.2 (3.8)	0.0 (ref)			0.0 (ref)	
	IYCF	249	16.6 (3.7)	IYCF	496	16.2 (3.7)	0.03 (-0.47, 0.53)	0.913	978	-0.02 (-0.48, 0.44)	0.944
	WASH	247	16.2 (3.9)	No WASH	494	16.3 (3.7)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	15.8 (3.6)	WASH	494	16.0 (3.7)	-0.37 (-0.87, 0.13)	0.143	978	-0.47 (-0.95, 0.01)	0.053
Central skinfold thickness, mm	SoC	246	10.8 (3.4)	No IYCF	493	11 (3.3)	0.0 (ref)			0.0 (ref)	
	IYCF	250	10.9 (2.7)	IYCF	496	10.9 (2.8)	-0.08 (-0.52, 0.36)	0.718	980	-0.02 (-0.44, 0.39)	0.915
	WASH	247	11.1 (3.3)	No WASH	496	10.9 (3.0)	0.0 (ref)				
	WASH & IYCF	246	10.9 (3.0)	WASH	493	11 (3.1)	0.10 (-0.35, 0.54)	0.671	980	-0.12 (-0.54, 0.3)	0.578
Hb g/dl	SoC	246	12.7 (1.3)	No IYCF	493	12.7 (1.2)	0.0 (ref)			0.0 (ref)	
	IYCF	250	12.6 (1.1)	IYCF	497	12.6 (1.1)	-0.04 (-0.20, 0.12)	0.624	980	-0.04 (-0.2, 0.13)	0.656
	WASH	247	12.7 (1.2)	No WASH	496	12.7 (1.2)	0.0 (ref)				
	WASH & IYCF	247	12.7 (1.2)	WASH	494	12.7 (1.2)	-0.01 (-0.17, 0.15)	0.865	980	0.01 (-0.15, 0.17)	0.911

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Sensitivity analysis

There was evidence of interactions between child sex and trial intervention arm for a few SAHARAN toolbox outcomes (Appendix table A7-3). Surprisingly, boys receiving IYCF had lower mental processing index scores than boys not receiving IYCF (-2.2 points, 95% CI -4.3, -0.2, p=0.028), while there was no evidence of a difference between IYCF arms for girls. There was weak evidence that girls receiving IYCF had better executive function compared to girls not receiving IYCF (4.4 points, 95% CI -0.0, 8.8, p=0.053). Boys showed no evidence of difference in Plus EF scores between arms.

For physical function, boys receiving IYCF had better grip strength than boys measured in the SOC arm (0.53 Kg, 95% CI 0.19, 0.87 p=0.002), whilst girls showed no difference between intervention arms. For VO_2 max, there was weak evidence that girls were performing worse in the IYCF only arm (-0.47, 95% CI -0.96, 0.01, p=0.057) compared to the SOC arm. However, girls also had a better VO_2max in the combined IYCF plus WASH arm, compared to the SOC arm(0.58, 95% CI 0.07, 1.08, p=0.025). Boys had no difference in intervention arms for VO_2max. There were also no significant interactions with child sex and growth outcomes for the SHINE interventions.

Detailed cognition and physical function subtests

Examining individual cognition subtests showed no evidence of differences between interventions (Tables A7-4 to A7-9). For the KABC-II, there was a minimal difference of 0.3 marks less in Atlantis Delayed for IYCF interventions and 0.6 marks in the learning domain (which comprises Atlantis and Atlantis Delayed subtests), but this was not clinically significant (Table A7-4). The small trend was unexpected since SQ-LNS has previously been shown to improve cognition[62]. The observed decrease in the SDQ total (Table A7-8) with WASH interventions was mainly concentrated in the emotional problems subscale.

The increase in grip strength was mainly observed in the dominant hand (Appendix Table A7-10). Detailed serial measurements of blood pressure after the shuttle run test was completed suggested there was a minimal additional reduction of ~ 2mm Hg in diastolic pressure for children in the WASH arm (Appendix Table A7-11). There was no difference in reactance or resistance bioimpedance measurements (A7-12)

A post-hoc analysis of absolute height suggested that children randomised to the IYCF arm had increased height with a GEE coefficient of 0.4 cm (95% CI -0.2, 1.0, p=0.197) . This was a similar magnitude to the benefit of IYCF at 18 months that was previously reported[73] (Appendix Table A7-13).

7.4 Discussion

This chapter examined the impact of early-life interventions in IYCF and WASH on school-age growth, cognitive and physical function in rural Zimbabwe. The SHINE trial was performed in an area with a high prevalence of stunting, poverty and adversity. The IYCF intervention included both complementary feeding education and daily small-quantity lipid-based nutrient supplements, which modestly reduced stunting and anaemia at age 18 months[73]. The WASH interventions had demonstrated no early-life impact[73]. The main objective of this chapter was to explore whether the interventions provided any sustained growth or benefits in function by the age of 7 years. Disappointingly, there was minimal evidence that the SHINE interventions improved school-age child cognitive, physical or growth outcomes. This is despite the increasing evidence of the benefits of SQ-LNS for short-term child survival, growth and neurodevelopment during the first thousand days[62]. The results from this chapter illustrate a need for policymakers to consider more comprehensive and longer interventions that include nurturing care to provide benefits across the life course.

There are remarkably few studies that have measured long-term (including school-age) function after IYCF or WASH interventions[76]. Data from the INCAP study in 1970's Guatemala illustrated how early-life improvements in nutrition could potentially provide long-term improvements for cognition[91]. However, 50 years ago severe stunting in Guatemala was much greater[5], the intervention was initiated earlier (for some participants it was during pregnancy) and hence the INCAP intervention had a larger impact on linear growth (+0.62 HAZ)[91] than the SHINE study (+0.16 HAZ)[73]. Small quantity lipid based nutrient supplements (SQ-LNS) are still viewed as the most effective complementary feeding intervention between 6-18 months of age to prevent stunting during this vulnerable growth window[105]. However, the overall beneficial effect size remains small: recent meta-analyses show SQ-LNS increases linear growth only by +0.11 HAZ[55]. There are also modest gains in early child development with standardised effect size of 0.11-0.13 SD when there is a high prevalence of stunting[64]. In Jamaica, a small effect on cognition was reported at age 6 years using milk-based formula[389], but the benefit was not observed at 18 years[390]. The (iLiNS)-DYAD study in Ghana recently showed a modest improvement of 0.16 Z-scores in socioemotional behaviour with SQ-LNS for children aged 5 years, measured using the Strengths and Difficulties Questionnaire[97]. However, the study also showed those randomised to SQ-LNS had reduced physical activity when measured by accelerometers, which may not be beneficial (although the authors postulated this was due to less restless behaviour[95]). There are clear widespread benefits from SQ-LNS in the short-term, but there remains limited evidence as to whether these observed early-life gains in growth and cognition may sustainably provide benefits as children become older.

This chapter has shown no long-term effects of SQ-LNS on cognitive function, despite using a broad battery of tests across a range of cognitive domains, all of which were piloted and adapted for use in rural Zimbabwe[192]. The primary analysis was unadjusted. This was not entirely unexpected, because no beneficial effects of SQ-LNS were observed on neurodevelopment in this cohort at age 2 years[77]. It was previously hoped that a greater benefit may be demonstrated for a broader range of cognition measurements at older years, but this ‘trajectory effect’ was not observed. It has previously been shown in multiple settings that an early-life growth benefit may not translate into sustained cognitive benefit: In a pooled analysis of 425 cohorts amongst 21

LMIC, the association between early life growth and educational attainment was weak and heterogeneous across countries, whilst the association between early child height and later adult height remained strong, [391].

The SHINE cohort had demonstrated improvements in linear growth in the IYCF arm at 18 months of age[73], hence it was also hoped that long-term benefits on physical function would be observed. However, only modest gains in hand grip strength following IYCF were displayed in boys. This was feasible given boys may be more biologically vulnerable to adverse conditions and more responsive to early-life interventions[259,356]. However, there were no other long-term increases in physical function measures such as broad jump or cardiovascular fitness. There were also no demonstrated benefits in growth or body composition measures such as lean mass, so potential mechanisms of the intervention effect remain unclear. It is possible that the high-quality protein in SQ-LNS may have improved muscle quality, which was not detectable by bioimpedance. Interestingly, in a post-hoc analysis, children randomised to IYCF had a GEE coefficient of 0.4 cm (95% CI -0.2, 1.0 cm) which was a similar magnitude to the benefit observed at 18 months[73]. This may suggest that the modest early-life growth benefit may be weakly detectable, although clearly a greater magnitude of benefit would be desirable. There was also no clear sub-population that benefited: In a post-hoc analysis, there was no significant difference in effects of the interventions among those who were stunted, compared to those who were not stunted, at 18 months (see Appendix table A7-14). Nevertheless, further verification from other studies of improvements from SQ-LNS in muscle growth, strength and quality would be an important result: sarcopenia predicts all-cause mortality during ageing[392] and hence improved school-age muscle function may indicate benefit across the life course.

The only benefit observed with the WASH intervention was a marginal improvement in the caregiver-reported child's socioemotional function, measured using the Strengths and Difficulties Questionnaire. Further sub-analysis showed this was mainly in the emotional problems scale. This was a cognitive domain that was more discernible by school age. The potential benefit of WASH on cognition has been previously postulated[393] but rarely observed[81], although few studies have recorded socioemotional outcomes. The WASH intervention in the SHINE trial was designed to decrease gut inflammation and reduce gut dysbiosis[135]. This could improve neurodevelopment in multiple ways through the gut-brain axis, including reducing inflammation and improving microbial metabolites[394]. However, the SHINE household-level WASH interventions did not demonstrate any improvements in child diarrhoea[73], growth[395], intestinal inflammation[396], or the composition and function of the gut microbiome[397]. Hence there is not a current biological explanation for any long-term benefits of WASH within the SHINE study. The few trials that have shown benefits for neurodevelopment also had corresponding gains in early-life weight[80] or reductions in infant diarrhoea[398]. One potential mechanism may be psychosocial in that the improved sanitation and washing facilities may have reduced the burden of work for mothers, who may have then been able to improve their nurturing care. This improved nurturing may then lead to long-term benefits for child socio-emotional function[81]; but there is no available data to explore this hypothesis.

The SHINE follow-up study has a number of strengths which support the result that SHINE early-life interventions had minimal sustained impact by school-age. The measurements are from a relatively large cohort of children successfully re-enrolled from the SHINE birth cohort, and using a toolbox which was extensively piloted[192]. The data collectors were also trained in detail, and monitored with regular quality control and standardisations.

There were also some limitations to the SHINE follow-up study, including using only one of the two original intervention districts, and being unable to monitor those who had moved out of Shurugwi. In response to this, it was reassuring that the baseline characteristics for those enrolled or not were broadly similar. In addition, baseline characteristics for those in SHINE follow-up between randomisation arms were also comparable. The sample size of 1000 children was designed to detect a 0.2 standard deviation in the mental processing index between intervention and control arms at 86% power at 5% level of significance. This was for unadjusted analyses. This was a reasonable sensitivity given similar magnitudes of benefit had been observed for parenting interventions[399], early-life stimulation[400,401], and conditional cash transfers[402]. All other associations explored were exploratory given they were statistically under-powered (including for the interaction testing). Nevertheless, the comprehensive battery of tests showed a consistent pattern of minimal long-term gains from either intervention. The large number of secondary outcomes increased the chance that the few benefits detected (eg for SDQ in WASH or grip strength in IYCF) were due to statistical type 1 error. Therefore further studies are required to confirm these findings.

The minimal functional benefits by school-age following the early-life SHINE interventions had three possible implications. Firstly, that the findings were genuine: SQ-LNS may not provide a long-term effect, because catch-up growth may have occurred in the other arms[100]. Similarly, WASH had no hidden benefits for school-age given no effect was observed on growth at 18 months[73] or on cognition at 24 months[77]. If this was the case, these results have important public health implications: they provide crucial evidence to design better in-depth interventions that have a greater magnitude of effect in early-life, and are implemented for longer. The second explanation was that a long-term benefit of the interventions was present but not detected due to the wrong tests being performed, low study power or poor sampling. However, the test battery showed important associations with early-life growth (see Chapter 5) and was extensively piloted[192], the sample size for unadjusted analyes appeared plausible for the effect sizes and no obvious baseline differences suggested a sampling bias. It remained feasible that a smaller impact of IYCF was missed due to the limited size of the SHINE follow-up substudy. The third explanation was that children may have been unable to benefit in a sustained manner from the IYCF intervention due to its short delivery time of 6-18 months, multiple adversities, COVID-19 disruption and challenges with nurturing care. A post-hoc analysis showed there was no particular difference in response to the interventions between children who were stunted or not, but future analyses may identify particular subgroups who benefited or had particular adversities that prevented this benefit being observed. However, it was more likely that the SHINE child's environment had a far greater impact on the child's development and growth[330], whilst growth itself remains a poor proxy for cognitive function[403].

In conclusion, this chapter has examined the impact of the early-life SHINE IYCF and WASH interventions on school-age growth, cognitive and physical function. The minimal impact of IYCF or WASH interventions observed by school-age, despite early-life growth benefits following SQ-LNS, provide important evidence of the need to improve interventions for long-term benefit. Recent meta-analyses show clear benefits of SQ-LNS for short-term growth, survival and early child development[61,63,64]. However, other meta-analyses have also shown the importance of including nurturing care and parenting interventions for child cognitive development[76,404-406]. Therefore, earlier interventions that also last longer and include nurturing care may be more effective at transforming the child's environment to provide long-term benefits for child growth and function.

8 Chapter 8: Discussion and Conclusions

8.1 Overview of results from SHINE follow-up

School-age growth, cognitive and physical function was measured in 1275 children from the SHINE cohort using the SAHARAN toolbox, which was first validated in a separate pilot study of 80 children[192]. School-age growth, physical and cognitive function has rarely been measured together in LMICs before, but evidence is growing that this time window from 5-14 years defines important trajectories in health and body composition[103], as well as increased mortality in LMICs [246]. The SAHARAN toolbox has provided several insights into the SHINE follow-up (SFU) cohort that may more broadly represent growth and functional trajectories across rural sub-Saharan Africa.

Comparative data was reassuring

Chapter 4 firstly examined data from 990 children who were born to women without HIV (CHU). Results using the SAHARAN toolbox were similar when compared to previously published cohorts. For example, cognitive processing from the mental processing index (MPI) of the KABC-II was similar to the rural Siyakhula cohort [190], fine motor function was similar to a Jamaican stunting study [205] and socioemotional function measured by the total from the Strengths and difficulties questionnaire (SDQ) were similar to UK norms [253]. Schooling results were also similar to the pilot study in Chapter 3[192]. Equally, physical function results in hand strength[254], leg strength[255] and cardiovascular function[219] all compared favourably to previously published results. Overall, the SFU dataset therefore appears to be representative of rural school-age growth and function within a southern African context, given comparable outcomes.

Child sex impacts school-age growth and function

An initial exploration of the impacts of child sex appeared to show that girls had better cognitive function in cognitive processing, literacy and numeracy, faster fine motor function and better socioemotional function. It was postulated that girls may have a cultural element driving them to concentrate more at school, or show more resilience within schooling[328]. Boys, by contrast, had greater hand strength[254,260] and cardiovascular fitness[219]. This was corroborated by observed differences in body composition, where boys had greater lean mass [261] and girls had greater skinfold thicknesses[407]. There were no observed differences in contemporary or baseline environmental factors by child sex. Overall, this initial analysis showed consistency with published literature on child sex.

Correlation analyses show importance of all functional outcomes

Correlation analyses showed that all outcomes of cognitive function were important to include in future analyses. A correlation coefficient of 0.64 between the complex MPI and the simpler school achievement test (SAT) illustrated the importance of schooling exposure and simple educational outcomes of literacy and numeracy to measure cognitive function at this age. Similarly, all outcomes of physical function were found to be important, although for growth outcomes, knee-heel length, impedance index and total skinfolds were removed from the principal components analysis due to collinearity.

Contemporary school-age growth associates with function

School-age head circumference, peripheral skinfolds, height and weight showed associations with cognitive function, potentially showing the importance of brain size and current nutritional status. Lean mass measures were only associated with physical function, whilst skinfold thicknesses were negatively associated with cardiovascular fitness. Hence school-age linear growth and lean mass accretion may be important to reduce the risk of chronic disease[177,408], whilst peripheral skinfolds and overall nutrition were more associated with school-aged cognitive function.

Principal components analysis provides growth, cognition and physical components

A principal components analysis derived 5 components loaded around nutritional status (PC1), cognition (PC2), physical function and lean mass (PC3), blood pressure (PC4) and bioimpedance phase angle (PC5) measurements, which represented 61% of the variance of the dataset. Hierarchical clustering of these principal components into 4 clusters showed a top cluster for growth and function (HCA 1) comprising children with better contemporary environmental, caregiving and nurturing conditions. Hierarchical cluster 3 (HCA 3) comprised children with relatively preserved cognitive function despite poor growth and physical function, potentially due to more girls and better caregiver education.

Contemporary factors influence cognitive function

To reduce multiple comparisons, the least absolute shrinkage and selection operator (LASSO) using generalised estimating equations (GEE) was performed on the principal components. This showed expected associations between contemporary environmental and nurturing factors and the cognitive function component (PC2) in particular. By contrast there were less associations with either the nutritional status (PC1) or the physical function components (PC3).

Early-life growth exhibits strong associations with later growth and function

Chapter 5 initially compared characteristics from baseline between mothers who were enrolled or not enrolled in long-term follow-up, to show that the follow-up cohort was broadly representative of the whole SHINE trial population. Important associations between early-life growth and school-age outcomes were also demonstrated. Length-for-age at 1 month and 18 months showed strong associations with school-age growth, some cognitive function measures, and particularly physical function (with strongest evidence for grip strength). Analyses that used 1 month LAZ as an exposure showed weaker associations with school-age outcomes, compared to analyses that used 18 month LAZ as an exposure, but still had observable associations with school-age grip strength and peripheral skinfolds. The stronger associations of early-life growth status with peripheral skinfolds may suggest that peripheral skinfolds are a more useful marker of an improved *quality* of growth, and hence also school-age function. By contrast, central skinfolds reflect centralised fat mass which is prioritised for survival by all children regardless of early-life growth status. Strong associations were seen between early-life head circumference (at 3 months and 18 months) and school-age cognitive function, peripheral fat and lean mass. Similarly, birthweight associated with later peripheral fat and measures of growth, whilst 18-month weight-for-age associated with school-age lean and fat mass. Low birthweight (<2.5 Kg) infants scored lower on all cognitive measures, but preserved their central fat mass, as has been previously reported[350]. Early-life mid-upper arm circumference had plausible associations with later lean and fat mass, as well as arm strength and function. Boys had a higher rate of stunting in the SFU cohort, as previously observed in longitudinal studies such as the Young Lives cohort[10], as well as the overall SHINE cohort[73]. This is potentially due to a complex interaction of social, environmental, and genetic factors antenatally[409,410].

Catch-up growth occurs but has minimal impact on function

Catch-up growth of approximately 1 Z-score from 18 months to 7 years was clearly demonstrated, although boys continued to have a higher risk of stunting. There was minimal catch-up in weight for girls, and a small catch-up in weight of 0.2 Z-score for boys. The catch-up growth itself had small associations with height and lean mass in girls, with small additional benefits for boys in broad jump and fine motor function, possibly because boys exhibited a higher prevalence of early-life stunting. Similarly, catch-up in weight of 0.2 Z-scores appeared to have some long-term benefit, with small increases in strength and lean mass for boys only.

Early-life factors influence physical and cognitive function

LASSO GEE was again applied to baseline environmental, maternal and child factors. Environmental and socioeconomic factors had plausible associations with the nutritional status (PC1), cognitive (PC2) and physical (PC3) principal components[318,319]. Antenatal influences were shown by maternal BMI being associated with all components. Maternal education, depression, parity and anaemia during pregnancy were plausibly associated with the cognitive component (PC2) [318]. Religion was also associated with multiple components, potentially due to the Apostolic faith being previously associated with lower socioeconomic status, reduced maternal autonomy[358] and health-seeking behaviour[359].

Children born HIV-free (CBHF) had more psychosocial disadvantage

Chapter 6 compared SAHARAN toolbox outcomes between children born to mothers without HIV (CHU) with children born HIV-free (CBHF) to HIV-positive mothers. Mothers with HIV had lower nutritional status during pregnancy, including lower haemoglobin and MUAC, as well as a higher parity compared to mothers without HIV, and markers of increased adversity, such as higher depression and food insecurity scores, and lower socioeconomic scores. Comparison of contemporary characteristics also showed fewer years of caregiver schooling and slightly higher depression scores, combined with reduced schooling exposure for the child.

CBHF had lower cognitive function, cardiovascular fitness and head circumference

CBHF had lower cognitive function for the MPI, SAT and Plus-EF executive function scores, which remained significant after separate models that adjusted for either baseline or contemporary covariates. CBHF also had lower scores for physical function, with strong evidence for reduced cardiovascular fitness. CBHF also had lower scores for growth and body composition, with strong evidence of difference in head circumference. A subgroup analysis by child sex suggested that CBHF boys had greater socioemotional dysfunction compared to CHU boys, and that CBHF boys had worse cardiovascular fitness than CHU boys, but girls were unaffected. This suggested potential additional vulnerability in CBHF boys. CBHF have previously been reported to have reduced cognitive function in early-life[376,377] but to date there has been little follow-up to school-age. Early-life differences in cognitive function persisted despite adjusting for baseline or contemporary covariates, suggesting a contribution beyond socioeconomic and psychosocial disadvantage. A biological difference is plausible based on the reduced head circumference, which may suggest structural brain changes. A reduction in grey matter volume in CBHF has been shown as early as 3 weeks of age using MRI[125], or diffuse tensor imaging combined with neuropsychological testing[380]. The ongoing impact from early-life growth is also observed in head circumference which represents growth particularly in the first 2 years[381].

The SHINE early-life nutrition interventions had minimal long-term impact

Chapter 7 explored the impact of early-life IYCF and WASH interventions on SAHARAN outcomes for 990 children born to mothers without HIV. There were no benefits of IYCF observed on MPI or any other cognitive outcome. IYCF was associated with a marginally increased handgrip strength (10.8Kg compared to a 10.6 Kg in the standard of care arm), which remained in adjusted analyses. There were no benefits of WASH observed for cognitive outcomes, except a slightly lower SDQ score by 1 mark. This was difficult to explain biologically since the only long-term follow-up of WASH interventions that had shown previous benefits had been accompanied by earlier benefits such as less infant diarrhoea[398] or early-life weight gain[80]. The SHINE WASH intervention has shown no benefits on growth[73], anaemia[73], enteropathogen exposure[395], intestinal inflammation[396] or microbiome composition[397]. For physical function outcomes, WASH had marginally reduced blood pressure observed in adjusted analyses only which was also challenging to explain scientifically. The most plausible explanation was type 1 error from multiple comparisons. There was no effect of either IYCF or WASH interventions on growth.

A pre-specified sensitivity analysis by child sex showed that the benefit from IYCF in grip strength was observed in boys only, possibly due to boys' greater sensitivity and hence responsiveness to early-life interventions [259]. Therefore it is better to review the disappointing long-term outcomes of the SHINE early-life interventions within the context of the strong associations of early-life and contemporary growth and conditions observed for the SHINE Follow-up (SFU) cohort.

8.2 Limitations

The SHINE Follow-up study has several limitations. Firstly, children were only re-enrolled from Shurugwi, one of the two study districts: Children from Chirumanzu were not included due to cost and logistical considerations. However, it is reassuring that baseline comparisons between those enrolled and not enrolled were similar, with no major differences that would drive a bias in potential results. Baseline factors were similar between randomised arms, which was also supportive of no obvious bias. However, no contemporary comparisons were able to be made between those enrolled and not enrolled, so it is not possible to definitively state that the SFU population was representative of the SHINE cohort. There is also the risk of further selection bias due to outward migration from the study area. Children who were still resident during school holidays were included to minimise the effect of outward migration, although those who were boarding at school may have increased exposure to education and may have come from more prosperous families. There may also be selection bias in SHINE Follow-up as relocations after the 18-month point may be related to greater food insecurity and lower household socioeconomic status. Survival bias is also a concern, particularly for CBHF who had a higher rate of mortality than CHU[388], although most deaths among CBHF happened in early infancy. It was also not possible to evaluate the impact of specific antiretroviral drugs due to the small numbers of CBHF exposed to alternative regimens.

Another limitation of SFU was the challenge in exploring the impact of violence and abuse within a context of limited social protection mechanisms. The COVID pandemic exacerbated risk factors for violence against women and children in the home in similar contexts in South Africa[411]. Another key outcome not currently explored is the impact of chronic stress, particularly on the HPA axis[82] or markers of inflammation or metabolic health at school-age. The exploratory analyses throughout this thesis were not adjusted for multiple comparisons. However, the consistent findings including the significance of early-life and contemporary growth and conditions, HIV-exposure and lack of impact of the SHINE early-life interventions does provide some reassurance that type 1 error is not driving the overarching themes described below.

8.3 Inferences and themes from SHINE follow-up

The importance of early-life growth

An underlying theme is the long-term impact of early-life growth and body composition on school-age function. The associations between contemporary growth and function seen in chapter 4 appear to be driven primarily by early-life growth (chapter 5), given the relatively small contribution from catch-up growth. Catch-up growth may still provide some later benefits for adolescence and adulthood such as reducing obstetric risk in girls, improving adolescent health, reducing chronic disease risk and potentially improving growth in the next generation. However, its functional benefit was not observed at school-age, suggesting early-life growth remains key to later function.

Differential impact of individual measures of early-life growth

Early-life head circumference

The individual measures of early-life growth were shown to be very important in reflecting *different* aspects of development. For example, linear growth in early-life was shown to be a poor proxy measure for later cognitive function[76] but had stronger associations with physical function. By contrast, head circumference as a measure of brain growth had associations with all direct measures of cognitive function, except socioemotional function (Figure 5-2). Beyond growth, cognitive function was highly affected by a range of other nurturing and environmental factors[1]. Therefore it is unsurprising that the relative size of associations with head circumference remained small, but worth noting that there was evidence for its importance across a range of cognitive domains. Within the complete SHINE cohort, IYCF modestly increased head circumference Z-score by ~0.07 at 18 months of age (95% CI 0.00 to 0.14 , p=0.043), but this effect was likely too small to significantly improve cognitive function in later life[73]. Therefore, head circumference appears to be a useful early-life measure of brain growth that associates with school-age function and should be reported as a priority in nutrition programming for early-life.

Early life height

At school age, height and other measures of lean mass were most associated with physical function (Figure 4-5). Linear growth in early life was also associated more strongly with school-age physical function than cognitive function (Figure 5-1)[306]. Interestingly, associations of linear growth were also observed with lean mass index (which corrects for the contribution of height to lean mass) suggesting a benefit of early-life growth to lean mass beyond that directly attributable to height. Lean mass was strongly associated with child height, consistent with the observation that stature was associated with strength of other muscles[307]. Lean mass includes functional skeletal muscle tissue, so it is logical that increasing height would be associated with greater strength. Therefore the previous focus of nutrition and agricultural interventions on maximising child height[147] may be more justified if purely focused on prioritising strength and long-term potential reductions in NCD risk.

Early-life Weight and MUAC

Early-life weight includes both fat and lean mass, hence there were associations with some aspects of school-age cognitive and physical function. Birthweight was associated with later lean mass and peripheral skinfolds, but 18-month weight alone did not appear sufficiently sensitive to predict school-age function compared to height and head circumference. Therefore weight appears a composite measure, with height and head circumference providing more information on early-life growth that relates to later function.

Early-life mid-upper arm circumference (MUAC) was associated with school-age lean and fat mass as well as arm function including grip strength, fine motor and executive function. However early-life MUAC was also not sufficiently sensitive to predict school-age outcomes beyond those related to arm function. Therefore early-life height and head circumference appear to be the most important anthropometric measures for monitoring the quality of early-life growth (and any response to interventions) in relation to school-age physical and cognitive function.

Insights from School-age body composition

Exploring body composition beyond anthropometry provided additional insights into the importance of peripheral fat mass as measured by skinfold thicknesses and peripheral body circumferences. These may associate with current nutritional status as well as longer-term cognitive function (Figure 4-4). Again, these observations were corroborated by consistent associations between early-life anthropometry (length, head circumference, birthweight and MUAC) and peripheral skinfold thicknesses (Figures 5-1a, 5-2a, 5-3a, 5-4a). It is well accepted that peripheral fat is lost more in severe malnutrition, whilst central fat is preserved for survival in children with growth faltering[38,212]. Central fat is prioritised by all children, including those with low birthweight and growth faltering, therefore it is logical that central fat was not associated with better early-life growth in the SFU cohort. Poor growth in early-life may represent reduced 'physiological capacity' leading to greater central adiposity and non-communicable disease (NCD) risk in the longer term[38,212]. Interestingly, peripheral skinfolds positively associated with handgrip strength, but negatively associated with cardiovascular fitness (Figure 4-5), suggesting overall weight from adiposity may hinder cardiovascular fitness but may provide benefits for strength. This is supported by the observation that in South Africa underweight children maintained cardiovascular fitness, but also lacked strength[313]. Hence there is clearly a balance between lean and fat mass to achieve optimal physical and cognitive function in childhood, which may differ between sexes, and is currently poorly understood.

Impact of child sex

Child sex continued to be an important determinant of growth, function and body composition at school age. The associations previously discussed remained in adjusted models that included child sex as a covariate, although it is apparent from table 4-1 that sex continued to be important: girls exhibited greater cognitive function and higher skinfold thicknesses, whilst boys exhibited stronger physical function with higher lean mass. Hierarchical clustering also suggested a group of children who preserved cognitive function despite poor growth, potentially due to increased caregiver education and a higher proportion of girls (Figure 4-7). There was also a sex difference in growth faltering and catch-up growth: boys exhibited a higher prevalence of stunting (Table 5-1), and higher rates of catch-up growth in weight (Figure 5-5), with marginally greater associated benefits (Figure 5-7). The increased vulnerability of boys compared to girls[356] was also apparent in reduced cardiovascular fitness, which affected male CBHF in particular (Table A6-8). In addition, boys exhibited increased benefits from the IYCF intervention for grip strength (Table A7-3). Taken together, future programmes that target child growth and function should examine individual effects split by child sex.

Environmental and nurturing factors influence child development

The importance of contemporary environmental exposures (including socioeconomic status, food security, adversities and presence of books) on the principal component related to cognitive function (PC2) was clearly demonstrated. This highlighted the importance of ongoing household support to promote children's cognitive development. Child factors were also important for cognitive function, particularly the amount of schooling received, child sex and child age. Similarly, the importance of nurturing factors (including caregiver education, depression, social support, caregiver relationship and discipline) provided important evidence of the need to sustain environments where nurturing care is prioritised throughout school-age. Of note, the principal component related to school-age physical function (PC3) appeared to be less susceptible to contemporary environmental exposures including schooling. This suggests that children's cognitive development may be more susceptible to contemporary environmental exposures than their growth or physical development. The public health significance of child function being associated with contemporary growth and conditions is that it highlights the importance of school-age for shaping later health and function. This has been relatively ignored until recently, hence being termed the 'missing middle' of childhood[245]. However, a recent systematic review highlighted that school-age remains a key period for interventions, with school-based interventions improving development and infectious disease outcomes, whilst financial interventions improved food security and school enrolment[412].

Early-life factors influence child physical and cognitive development

Early-life factors including socioeconomic status, maternal employment and dietary diversity were associated with the cognitive principal component (PC1), similar to contemporary factors. However, a notable difference was that more baseline environmental exposures (employment, food security and household size) were associated with school-age physical function and lean mass (PC2), in comparison to contemporary factors. This may suggest that early-life environmental exposures had more effect on growth and lean mass than later environmental exposures. It may be that early-life environmental exposures set antenatal growth, cognitive and physical function trajectories, but contemporary exposures continue to have an important influence on school-age cognitive function. Hence this provides further evidence of the need to continue to support children and families to ensure cognitive development throughout school-age.

Maternal factors (including education, parity, haemoglobin and depression) were all associated with school-age cognitive function. However, only maternal BMI was associated with school-age physical function. Again, this suggested that cognitive function was more susceptible to maternal early-life exposures than were lean mass or physical function. As expected, maternal BMI associated with birthweight, lean mass and subsequent physical function. Household religion appeared to be important in both cognition and physical function. This may represent further opportunities for engagement, particularly among members of the apostolic faith in Zimbabwe[359]. Marital status also impacted all components of growth, physical and cognitive function. This may have multiple mechanisms of action including improved antenatal and postnatal nutrition, as well as ongoing support for the child. Marital status may be an indicator of vulnerability within a rural Zimbabwean context. However, caution should be applied to over-interpreting the principal components given that they only represent 61% of the variance in the dataset.

Benefits from SHINE IYCF interventions were not sustained

A final theme was the disappointing long-term impact of the SHINE early-life WASH and IYCF interventions, despite these being carefully designed following formative work[73]. There are three potential explanations for this, including a genuine lack of effect, failure to detect a difference in the substudy, or that children were unable to respond; overall, it seems most likely that there was no intervention effect. The baseline comparisons suggested that the children selected into the SFU cohort were representative, and the sample size was sufficient to detect a plausible effect, whilst post-hoc analyses suggest that stunted children at 18 months did not respond any better than those who were not stunted. These results suggest that the hope of increased trajectory effects from early-life interventions was too optimistic in this context. However, reassuringly the results also provided no evidence of any adverse effects from SQ-LNS supplements. This finding supports the lack of central adiposity from SQ-LNS that has been previously noted elsewhere[114,413]. Recent meta-analyses have shown that SQ- LNS continues to have clear benefits for short-term child growth[61], survival[62], anaemia[63] and child development function[64], which has led to calls to scale up SQ-LNS as part of IYCF programmes[414]. SQ-LNS may also provide greater benefit in the future as its formulation continues to be refined[415]. However, these calls are not without controversy over commercialisation of complementary feeding, lack of local empowerment and concern of appropriate control groups for comparison[416].

It is plausible that children in the SFU cohort were unable to benefit fully from early-life IYCF due to a range of unmeasured constraints (see section 8-4-4). A key limitation was measuring adversities in a simple binary way, without exploring the child's susceptibility to these risk factors (see Figure 8-3). It was unsurprising there was no clear benefit from the WASH intervention, given no early-life benefit was demonstrated, but IYCF had previously shown a benefit in growth and anaemia[73]. This was broadly consistent with meta-analyses demonstrating the global benefit of SQ-LNS in multiple settings[62]. Within the SFU cohort, a post-hoc analysis of absolute height showed that children in IYCF arms had very weak evidence of long-term growth benefits (0.4 cm, 95% CI -0.2, 1.0, p=0.197). This absolute height gain was similar to the absolute growth benefit previously reported in SHINE following the IYCF intervention at 18 months[73]. Therefore, it is possible that the growth benefit ended at 18 months, once SQ-LNS was stopped. Hence continued SQ-LNS supplementation might have provided ongoing benefits for catch-up growth in height. Continued growth with ongoing SQ-LNS was demonstrated in a recent supplementation trial in 1- to 5- year-olds in Uganda[417]. There was also no difference in school-age haemoglobin levels following the IYCF intervention (Table 7-3), which is unsurprising since this is highly affected by contemporary nutrition[418], and anaemia was rare at school-age. Overall, these disappointing results following early-life WASH and IYCF interventions remain valuable for the insights they give to planning future interventions.

8.4 Designing better interventions from SFU

The need for more successful interventions

There is an increasing need for better interventions to ensure children grow and develop to their full potential: The COVID-19 pandemic had a deleterious impact on child health and development, through a variety of mechanisms including school closures, loss of livelihoods, lack of immunisation, increasing food insecurity and mental health concerns including anxiety and depression[419]. The impact of school closures in disrupting children's education was also demonstrated in Shurugwi district[325]. Climate change is also an increasing global public health challenge that threatens child development, physical and mental health[420]. The SHINE cohort is predominantly rural, but climate change is likely to increase pressures on subsistence farmers. Relocation may lead to disruption of key familial and community relationships, with potentially increased exposure to poor living conditions and social instability, which may further undermine mental and physical health[421]. There are increasing concerns that progress in child, adolescent and maternal health have been reversed[422]. These factors may combine in syndemics of undernutrition, obesity and climate change causing global nutrition dysfunction[423]. Within this, exposure to stunting is thought to be a key driver for later non-communicable disease, particularly in LMICs[15]. These combined risks particularly affect the most vulnerable children and households[422]. Therefore, the continued risks to child development mean that evidence for more effective interventions is urgently required. Clearly, interventions need to provide a greater magnitude of benefit, that is sustained into school-age.

a. Earlier interventions

The SHINE trial interventions did not specifically target pregnancy or pre-conception, both of which are important windows for intervention to improve birthweight, which has lifelong implications. Although a latrine was built during pregnancy for households in the WASH arms of the SHINE trial, this was unlikely by itself to improve maternal outcomes (see later). The International Lipid-based Nutrient Supplements (iLiNS)-DYAD trial showed that LNS targeted to both mothers and then their infants improved growth at 4-6 years, if the mother was not overweight[413]. There is increasing evidence that antenatal nutrition interventions (including multiple micronutrient supplementation and balanced protein and energy supplementation) have benefits, particularly for small and vulnerable newborns[424]. Other interventions to prevent low birthweight and prematurity include low-dose aspirin, support for smoking cessation, malaria prevention, treatment of asymptomatic bacteriuria and syphilis, as well as progesterone provided vaginally[424]. Similarly interventions that target maternal education, decision-making, antenatal care and general support could also reduce the prevalence of low birthweight[425]. Novel future strategies may also include improving dentition[426] and reducing maternal inflammation in other ways[427]. All of these could be combined to reduce preterm and small-for-gestation-age babies and increase birthweight, which could then be combined with further interventions in early childhood. Secondly the period from 0-6 months is the most vulnerable window for incident stunting[24], although evidence-based interventions to improve feeding and nutrition during this time are scarce. Some promising work includes improving maternal wellbeing and aiding relaxation to improve breastmilk supply[53], but overall there is a dearth of research and innovation in this area.

b. Deeper interventions

The SHINE WASH intervention had no impact on child growth[73], and was not successful at reducing the burden of enteric infections[428], markers of environmental enteric dysfunction[396], or the composition and function of the gut microbiome[397]. WASH clearly remains important for child health and development, but household-level interventions did not have the expected impact. Analysis of similar trials has suggested that WASH interventions require 'deeper' (i.e. more intensive) implementation in order to derive a benefit: a review of the literature suggested that handwashing and water treatment interventions should be at least fortnightly in order to achieve effective behavioural change that reduces diarrhoea[395]. WASH Benefits Bangladesh health promotion visits occurred six times a month, and the study reported benefits for diarrhoea and later cognition[78], but comparison was made with a control arm that had no visits. There is also a call for 'transformative WASH', that provides a more comprehensive package of interventions to reduce enteropathogen burden[429]. This could include local measures that more effectively separate animals and their waste away from household living areas[430]. In addition, water interventions may need to increase both volume and accessibility to water[429]. Beyond this, long-term and large-scale improvements in water and community-level sanitation may be required: a natural experiment around a Gambian research station showed that child growth was only optimised for children with piped water into the home combined with good quality housing, whilst socioeconomic status alone had a relatively minor impact[431]. Overall, WASH interventions need to be designed to have a much deeper impact to provide benefits for child health, growth and function.

c. Longer interventions

It is widely accepted that the contemporary environment continues to influence child growth and development in multiple ways[247]. For example, food security[248], adversity[249], caregiver support[250], nurturing care[251] and schooling exposure[252] may all be associated through multiple mechanisms with school-age child growth and function. There is also evidence that BMI at school age is affected by the quality of the diet[103,432]. One systematic review suggested sustainable school-based feeding and exercise regimes are key in addressing underweight among rural children as well as overweight children in urban South Africa [433]. However, the majority of studies in this review were cross-sectional with a noted dearth of longitudinal studies from early-life[433]. The results from SHINE suggest that child growth and function are associated with contemporary level conditions, which provides further evidence that interventions should continue to provide support through to school-age.

There is increasing interest in interventions that focus on several developmental periods to provide a more sustained and greater impact. For example, the Healthy Life Trajectories Initiative (Bukhali) trial in South Africa used community health worker-facilitated support for behaviour change from preconception through infancy to childhood[434]. Another successful example from India is the Women and Infants Integrated Growth Study where health, nutrition, psychosocial care and support, and WaSH interventions were delivered during different combinations of preconception, pregnancy, and early childhood periods[435]. Interestingly, the most impressive results for reduction of both low birthweight and child stunting were in the intervention that delivered throughout preconception, pregnancy and early childhood[435]. The SFU results in this thesis may provide further evidence for the need for longer intervention into school-age.

Older children may also benefit from behavioural and socioemotional interventions, although the common fadeout of effect of promising behavioural and socioemotional interventions has previously been noted[436]. Their lack of sustained success also provides a useful framework to analyse effectiveness of long-term interventions[436]. Interventions can be characterised as firstly 'skill-building' which fundamentally provide better support and coping strategies throughout life. Secondly they can also be 'foot-in-the-door' which are focused to equip a child or caregiver to deal with specific risks at a specific time[436]. Thirdly they can alter environments in a sustained way, which ultimately provide the enabling environments to ensure early gains are sustained into the longer term[85]. Therefore interventions need to continue to support school-age growth and development.

d. Broader interventions

Interventions should target caregivers and mothers in early-life. There is ample evidence of positive benefit from maternal interventions targeting a range of areas including maternal mental health and women's empowerment[437]. This can include conditional cash transfers, WASH and agricultural interventions as well as antenatal nutritional supplementation and breastfeeding promotion[437]. Of note, a recent review of reviews noted that their effectiveness was increased if combined across multiple sectors[437]. For example, a recent randomised trial has shown that improving nutrition education and providing vegetable seeds for pregnant women in Ethiopia, combined with involvement of their husbands provided a significant increase in birthweight compared to controls[438].

Nurturing care interventions are key to cognitive development and were missing from the SHINE early-life interventions. Nurturing care is defined as providing stable environments that promote children's health, nutrition and learning, and protect from adversities[251]. Integral to this is nurturing responsive, emotionally supportive and developmentally enriching relationships between the child and caregivers[251]. A systematic review of 14 different nurturing care interventions noted a pooled effect size of 0.38 to 0.48 standardised mean difference (SMD) compared to nutrition interventions alone with a SMD (0.05 to 0.08)[76]. One of the few long-term follow-up studies from weekly visits to encourage caregivers to give psychosocial stimulation in Jamaica noted a 25% increase in salary 20 years later. This enabled stunted children to catch-up in later earnings with a non-stunted comparison group[92].

Promoting and facilitating nurturing care across the life span should lie at the centre of future interventions[439]. Hence the nurturing care framework has been extended from early childhood to adolescence[251]. Recent meta-analyses show that effect sizes for improving child development are impressive for parenting interventions[404] across all incomes[399].However, nurturing care should ideally be part of a comprehensive set of interventions: one meta-analysis of nurturing care interventions showed they may not improve growth effectively without combining them with nutrition interventions[76]. Therefore interventions should incorporate sustainable ways of providing nurturing care.

‘Capacity to benefit’ and ‘Capacity to respond’

The short-term benefits of SQ-LNS have been demonstrated in multiple contexts[62]. As the most successful stunting intervention to date[62], SQ-LNS interventions provide additional insight into how to plan for successful interventions. An important concept applicable for all interventions is categorising subgroups into ‘potential to benefit’ and ‘potential to respond’ [62]

- ‘Potential to benefit’ is defined where certain subgroups of children are more likely to benefit from interventions, typically due to greater deficits at baseline. For example, in a recent meta-analysis of 14 randomised trials of SQ-LNS including 37,000 children, there was greater benefit for SQ-LNS for children from households with lower socioeconomic status and in areas with a higher proportion of stunting[62].
- ‘Potential to respond’ is defined where certain subgroups differ in their response to an intervention. For example, in the meta-analysis of SQ-LNS[62], children with greater inflammation were less able to respond, as were households who had lower maternal levels of education[62].

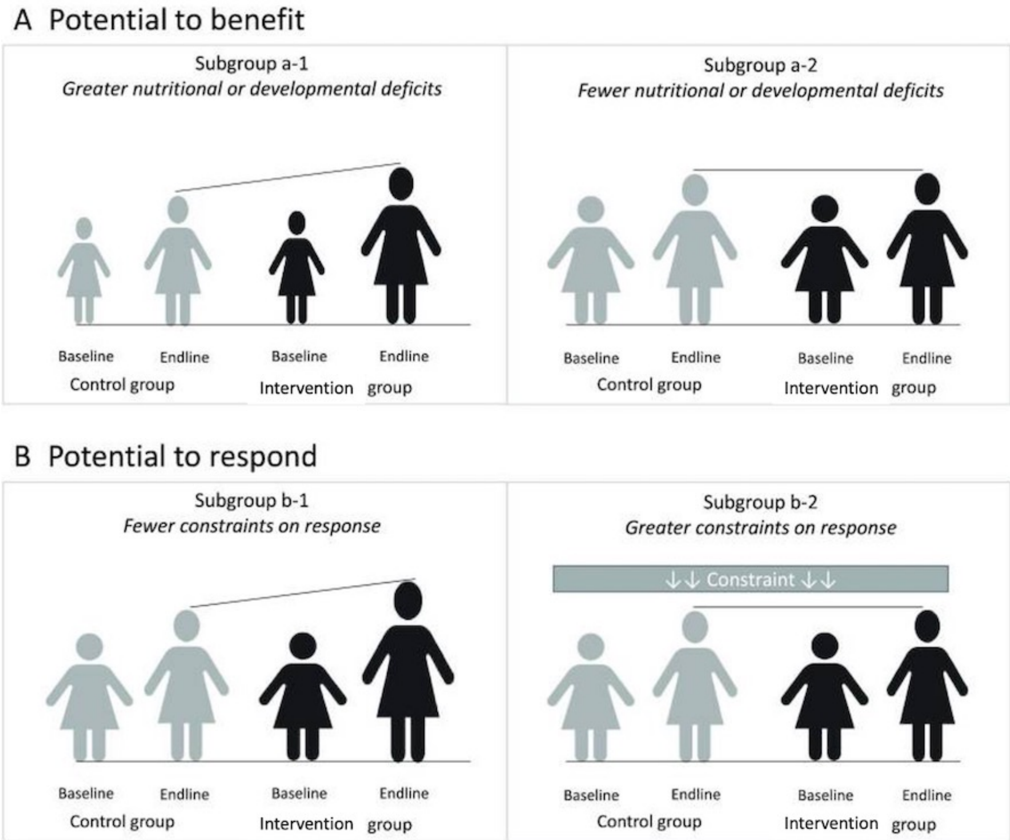


Figure 8-1 Potential to benefit or potential to respond to interventions

The response to interventions may be characterised into A) Potential to Benefit, where greater deficits (eg lower height or greater deprivation) at baseline may provide an improved benefit of an intervention. Or B) Potential to respond, where greater constraints (eg inflammation or lack of education) may provide additional constraints to limit a response.

Future trajectory analyses of the SHINE cohort may be able to identify sub-groups of children who responded most to the IYCF intervention. In early-life, CBHF appeared to benefit more in height than did CHU, following the IYCF intervention[141], and showed benefits for child development following the combined IYCF+WASH intervention[142], in contrast to CHU. This study has also shown that CBHF remained more vulnerable by school-age. However, scaling up additional support for CBHF at school-age whilst avoiding HIV exceptionalism represents a challenge[440]. Moreover, by school-age, the long-term benefits of targeting those most vulnerable were less clear: children already stunted at 18 months did not appear to have an additional benefit, and no obvious benefit to intervention was noted when analysing the data by hierarchical clustering. The effect of child sex may also be important: the meta-analysis of 14 trials of SQ-LNS show that girls had a greater ability to respond to the SQ-LNS in growth[61]. This was attributed to boys having greater constraints due a greater risk of morbidity and mortality in early life and more vulnerable to environmental stressors[441]. By contrast, the IYCF intervention in SHINE showed a benefit in handgrip strength that was primarily in boys, potentially due to their poorer initial growth enabling a greater capacity to benefit. Targeting interventions to the children most likely to benefit from response and capacity may be one step. However, it also raises concerns of how to deal with whole communities that exhibit varying degrees of poor growth and development and raises concerns of equity and cut-offs for intervention. An alternative approach examines individual child responses by examining the susceptibility for each child to adversities which hinder optimal growth.

8.5 Future directions for research

Characterising individual susceptibility of children

Some children living in poverty and with adversity may develop as well as peers living in more favourable conditions, whereas others will show cognitive delays, reduced growth, physical function or other impairments. Children may respond differently to their environments due to susceptibility from both genomic variation and other intrinsic child factors, such as temperament and neurobiological responsiveness to stress[82]. Susceptibility may be defined both within the inherent sensitivity of the child, as well as broader community factors.

Interventions are designed to mitigate the effect of adverse environmental conditions that drive poor child growth and function. Exploring main or average effects of the impact of adversity within a cohort may also ignore the highly variable outcomes of children living with similar levels of adversities. A more nuanced approach to adverse events looks beyond measuring adverse child experiences (ACEs) to explore the social ecology of childhood[442]. Bronfenbrenner's Ecological Systems Theory provides a model for theorizing how the complex, hierarchically organized systems in societies can interact with a child's life, with a rich interplay between systems mitigating or exacerbating the effects of early life adversity[442]. For example, a potential exacerbating or protective factor within adversity is the family. There is increasing understanding that negative caregiving, early-maladaptive schemas and mental health have complex connections and inter-generational pathways[443]. In addition, school, peers, faith communities and the neighbourhood construct the microsystem which interacts with the child and also the broader macrosystem of community and society (Figure 8-2).

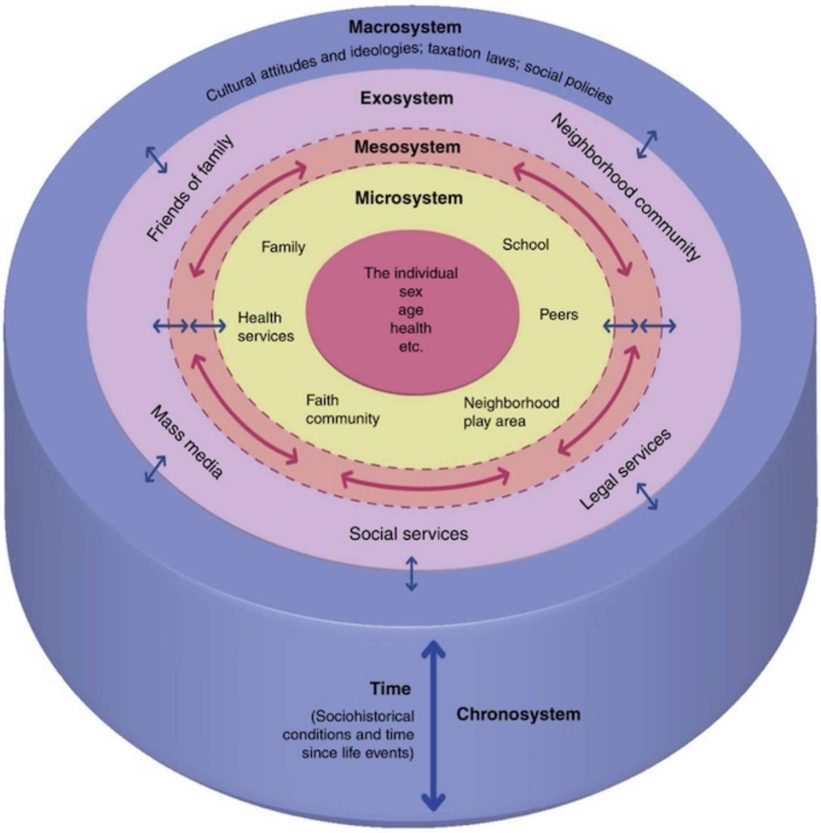


Figure 8-2 Bronfenbrenner's Ecological Systems Theory

Bronfenbrenner's Ecological Systems Theory describes how the complex, hierarchically organized systems in societies can interact with a child's life. In particular, it describes the interplay between systems that mitigate or exacerbate early life adversity[442]

Cumulative effects on early child development of individual adversities categorised into socioeconomic, maternal, nurturing and child have been noted in the SPRING trial in India[227] as well as the USA[444]. Other models suggest adverse outcomes effect the poorest children in a non-linear manner[445]. Although cumulative models are important for understanding toxic effects of poverty in some contexts, they may also conceal unique effects of individual risks and overlook important interactions among risks[82]. Hence cumulative effects should be considered in parallel with models of mediation and moderation that crucially include the child's innate sensitivity[82].

Counting ACEs as a method for understanding early life experiences paints a two-dimensional picture of the many interacting factors that comprise a growing child's multi-dimensional environment (Figure 8-2). ACEs do not always carry the same emotional weight or elicit similar distress levels between children, therefore binary "yes/no" responses of events that occurred do not accurately represent their impact on an individual child, which is mediated both by context and the child's innate susceptibility[446]. Beyond the more severe adversities represented by ACE, there are also multiple preventable sources of early life stress (ELS) which may include food and housing insecurity, bullying, discrimination, inattentive parenting, or family separations. These stresses are not routinely measured due to the lack of validated, objective metrics that can be assessed longitudinally. Therefore, a key step is to try and elucidate the impact of adversity on the child within the context of risk and protective factors.

Children exhibit a wide range of differential susceptibility based on intrinsic child factors (sex, age, health, sensitivity) and broader extrinsic factors (caregiver, family, contextual and cultural), as well as characteristics of the adversity (timing, intensity and duration) (Figure 5.3).

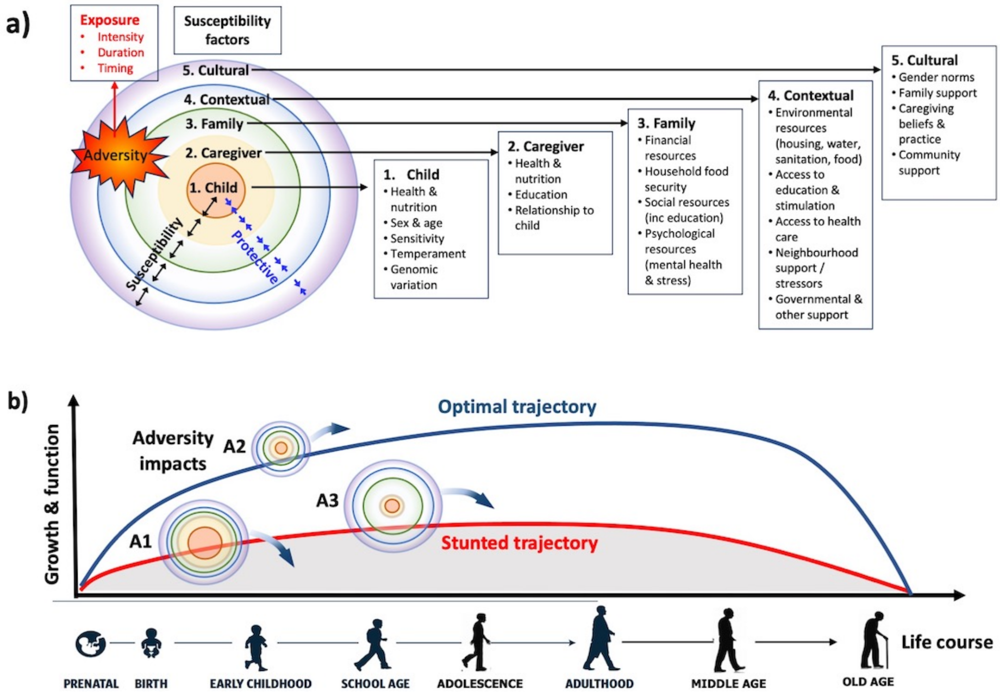


Figure 8-3 Differential susceptibility of children to adversity

Differential susceptibility of children to adversity depends on a range of child, caregiver, family, contextual and cultural factors. A child's susceptibility is illustrated as a multi-layered circle, in which each layer is a category of susceptibility factors, and the size of the circle represents the child's overall susceptibility. Susceptibility factors increase the overall susceptibility, whereas protective factors decrease the child's susceptibility. Effect moderators can interact to affect child vulnerability and resilience. The size of each susceptibility will also affect the impact of adversity as demonstrated in b) Different susceptibilities to adversity may affect child growth and development trajectories in different ways: A1: high child and caregiver susceptibilities to adversity in early life result in reduced child trajectories. A2: Low susceptibility to adversity results in little impact on the child trajectory A3: Low child and caregiver susceptibilities to adversity in later life may be overridden by high family, contextual and cultural susceptibilities that drive a reduced trajectory.

Susceptibility to adversity: Intrinsic child factors

Evidence is accumulating for the importance of the sensitivity[447] and temperament[448] of the child, which can mediate the effects of adversity. Intrinsic child factors also include the child's health and nutritional status which clearly confer greater resilience[393]. Child sex is also important; boys appear to be more sensitive to poor growth, potentially in response to different immunological function and also cultural expectations[259,410]. The child's age and developmental stage may also shape the effects of adversity. A younger age may have biological markers of greater sensitivity: this was shown recently in a DNA-methylation study, where specific adversities in early and mid-childhood were associated with epigenetic changes of premature biological ageing[449]. Telomere length was also associated with early-life adversity[450]. Both of these are mechanisms for 'biological embedding' describing stable epigenetic modifications which shape individual response to later adversities[85]. Underlying this sensitivity is genomic variation. For example, genetic polymorphisms in monoamine-regulating genes confer differential susceptibility to adversity[451]. This was shown to affect the response to interventions in a trial to support maternal-infant attachment in South Africa[452]. Therefore child intrinsic factors work in multiple ways to mediate susceptibility to adversity and to interventions.

Child susceptibility to adversity: Extrinsic environmental factors

Extrinsic environmental factors that shape susceptibility to adversities and interventions include caregiver, family, contextual and cultural factors[453]. Improved caregiver education may improve diet[454], healthcare seeking[455] and involvement in stimulation and welfare programmes which in turn improve child growth and development[453]. Poor financial and psychological resources increase stress in parents and may amplify adversity[445]. Wider societal and cultural influences may also mitigate or exacerbate adversities[456], with lifelong effects[457]. There are also neuro-behavioural effects which can cascade to problematic behaviour. This behaviour may drive further adverse experiences, which may combine with poor mental and physical health[85], to generate so-called 'developmental cascades'. Biological markers showing the impact of chronic stress include the hypothalamus, pituitary and adrenal (HPA) axis, particularly cortisol. Highly responsive caregiving has been shown to result in a lower risk of elevated cortisol in the child from adversities[458]. Therefore extrinsic environmental factors also shape the child's response to adversity, as observed with biological markers such as cortisol. Overall, a detailed measurement of psychosocial susceptibilities to adversities would provide valuable insight into the efficacy of interventions. This should include both the child's intrinsic susceptibility as well as the surrounding caregiver, family, contextual and cultural environment factors. Further insight can be obtained by combining this with biological markers of susceptibility such as cortisol levels.

Characterising biological markers of dysfunction

An appraisal of the SHINE trial and other nutrition intervention trials suggest there is considerable room for improvement, particularly because the underlying mechanisms driving faltering growth and development remain poorly understood. Exploring underlying mechanisms including inflammation, combined with understanding an overall framework of contributing factors and their interactions may assist design of more effective interventions.

Inflammation

Inflammation is a key issue that has not been targeted so far to improve child growth and function. Inflammation has previously been shown to be high in Zimbabwean[40], Tanzanian[459] and Malawian[460] children with stunting. Interestingly, this inflammation was accompanied with a concomitant decrease in growth hormones[40 460]. Growth failure may be preceded by markers of systemic inflammation, which may arise from the gut[461]. Studies have also shown that febrile illness[462] and pro-inflammatory cytokines are associated with lower child neurodevelopmental scores for Bangladeshi infants living in poverty[463]. Therefore it is likely that inflammation plays a key mediating role in inhibiting child growth and function[463].

(Figure 1-4).

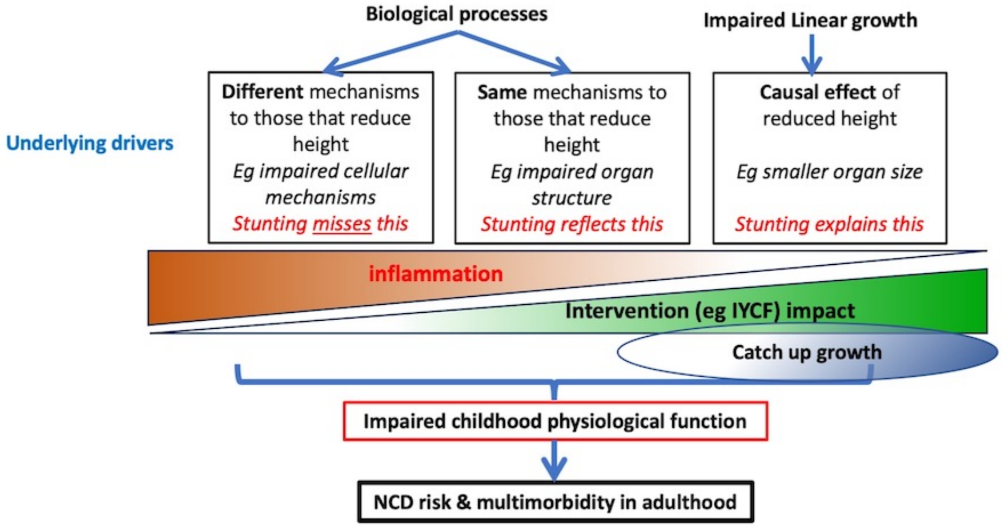


Figure 8-4 Underlying drivers of impaired linear growth

Underlying drivers of impaired linear growth comprise biological processes that reflect reduced structure but also other cellular processes. Inflammation may drive this and interventions such as IYCF may aim to mitigate this. Catch-up growth may also have an effect on some parameters. Impaired childhood physiological function reduces physiological capacity and hence drives NCD risk and multi-morbidity in later life.

Stress due to challenging living conditions has also been observed to increase systemic inflammation markers including CRP and IL-6[464], which may mediate the negative effects of stress on cognitive function[465]. Altered cortisol signalling may also mediate the association observed between poverty-related risks in the USA (such as low income and low maternal education) on the child's cognitive abilities[466]. Similarly, caregiving experiences also mediate the effect of poverty on structural imaging of the hippocampal volumes in children[467]. The inflammatory signal associated with psychological trauma continues into mid-childhood[468], adolescence[468], and into adulthood [469]. The dysregulated HPA axis may also affect metabolic processes by diverging energy from synthesis towards chronic inflammation[82] as well as later psychopathology in children such as depression[470]. There is even some emerging evidence that early-life stress may alter the microbiome[471].

Inflammation also elevates cortisol levels, which may lead to long-term dysregulation of the HPA axis[470,472]. Chronic low-grade inflammation likely acts across the life course, and has been implicated in the progression of non-communicable diseases[23]. However, measures of growth may only capture a small part of the biological processes involved (Figure 8-4) so a more detailed assessment may be required.

Mediation and moderation of effects

Designing effective interventions requires an in-depth understanding of the biological pathways that contribute to poor growth and function, which is still lacking[82]. Effective interventions for child growth and development likely require multi-faceted strategies that target the multiple interactions between adverse environments and the body's response.

Biological pathways may describe three different types of interactions: mediation, cumulative effects and effect moderation[82]. Mediation is defined when a risk factor affects child growth or development via another factor. Often these are grouped into distal factors such as socioeconomic status, and more proximal factors such as nurturing care. Cumulative effects are when multiple or chronic risks have an additive effect providing a cumulative burden, such as has been observed for multiple early-life child adversities in the SPRING cohort in India[227]. Effect moderation occurs when effect is determined by the presence of a third factor. Intrinsic factors such as caregiver education or child sensitivity to different stressors may moderate how a child responds to different risks or interventions.

Key initial exposures include:

i) Psychosocial risks from stressful environments and adversities

ii) Nurturing risks from poor child-caregiver relationships and lack of stimulation

iii) Antenatal risks from maternal health, growth and nutrition

iv) Pathogen and toxic risks from the environment

v) Malnutrition risks from poor diet

These then interact through multiple pathways including[82]:

i) Neuroendocrine stress activation resulting in increased allostatic load, particularly through the HPA axis.

ii) Immune activation in response to infection resulting in acute inflammation

iii) Immune activation in response to chronic subclinical infection and stress resulting in chronic inflammation and dysregulation,

iv) Energy metabolism and nutrition that affect physiological and neural growth and later function.

v) Gut microbiome and function which impact absorption and inflammation

These pathways then impact the child's growth, physical and cognitive function and later risk of chronic disease (Fig 8-5).

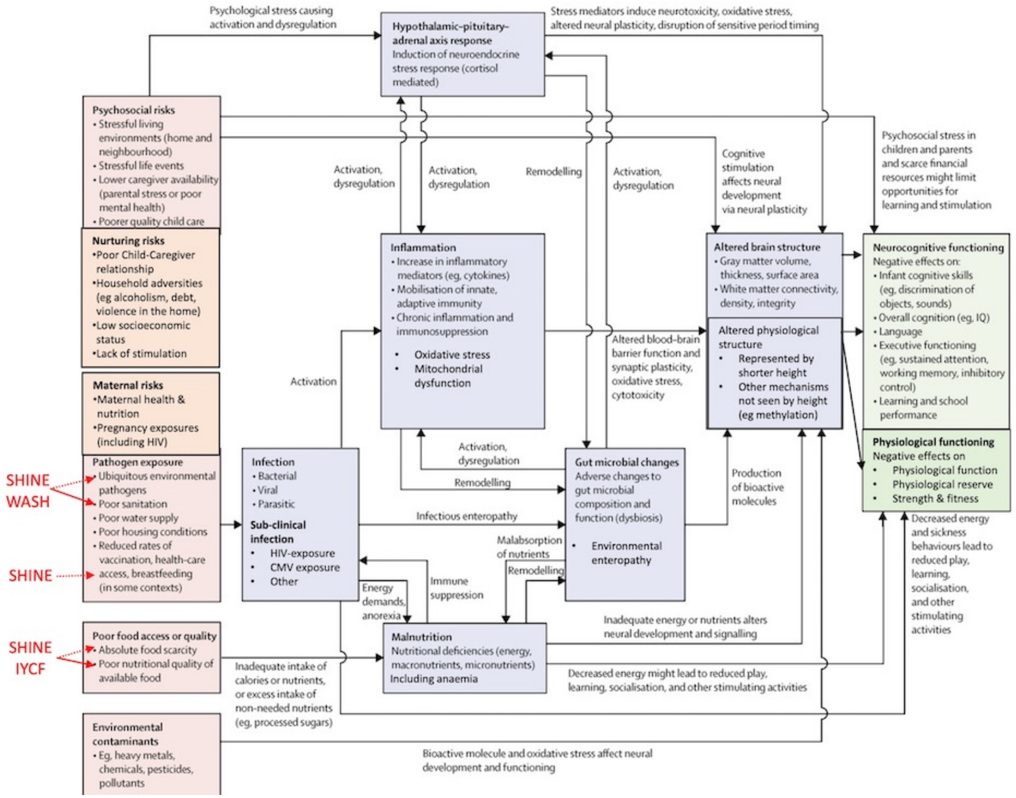


Figure 8-5 Potential biological pathways that mediate effects of poverty risks on child growth and development, adapted from[82].

There are multiple interactions among key poverty-related risk factors, focusing on biological pathways related to malnutrition, infection, inflammation and the neuroendocrine response to stress. Potential interventions from the SHINE trial are also demonstrated in red, although the WASH interventions had minimal evidence for impact on diarrhoea or enteric pathogens. SHINE did improve rates of breastfeeding across all arms, but this did not significantly improve levels of early-life stunting. Adapted from [82].

The potential interventions from the SHINE trial are marked but had little impact: SHINE WASH interventions were unsuccessful at reducing enteropathogens[395], inflammation[396] or improving the microbiome[397], growth or anaemia[73]. SHINE did improve rates of breastfeeding across all arms, but this did not significantly improve levels of early-life stunting[73]. The SHINE IYCF intervention helped to mitigate malnutrition and improve early-life growth[73] but had no major observable impact on physiology or function by school-age (except for a marginal improvement on handgrip strength in boys). Early-life markers of gut inflammation were unaffected[396] so it is unlikely there were broader effects on inflammation or the HPA axis, although this was not measured.

Water insecurity had a minimal impact on SAHARAN outcomes when measured using the household water insecurity experiences scale (HWISE) contemporary questionnaire[473]. However, this only measured water insecurity in the past month[473], so may not have detected variability in water insecurity between years and seasons. Shurugwi is also a mining district, so there may also have been differential exposure to environmental toxins (particularly through water) which was not measured[82,474]. There may have been a range of psychosocial risks and stresses for both caregiver and child that were not detected using the child parent relationship score alone[229]. Finally, for children born HIV-free, it has been shown that both inflammation and Cytomegalovirus (CMV) viraemia affect early-life growth[475], so CMV viraemia and potentially other early-life infections should be investigated where available.

Future work within the SHINE follow-up cohort

The SHINE Follow-up cohort is currently being assessed at 8-9 years of age, with a shorter 1-hour annual visit which will provide trajectories of growth, handgrip strength and literacy and numeracy in early school-age. In addition, child illness has been monitored in a sub-study by monthly morbidity recall over approximately 1 year which will give rates of illness and healthcare seeking behaviour. This may differ for CBHF compared to CHU.

Additional funding has been obtained for detailed characterisation of the physiology of SFU children at 10 years, including lung function, cardiac ECHO, renal ultrasound, peripheral quantitative CT (to measure muscle and bone structure) as well as metabolic blood tests including hair cortisol. In addition, a Hyperfine low-field MRI machine will provide brain MRI imaging, which will be combined with repeat cognitive testing. Event-related potentials (ERP) will be measured through EEG recordings during a psychometric task, in a sub-study examining the difference in cognitive function between CBHF and CHU. Finally, a detailed caregiver and child questionnaire will examine child and caregiver wellbeing and mental health. In addition, family, societal and schooling factors will be asked to build a model of the social ecology around each child, employing Bronfenbrenner's Ecological Systems Theory. Hence detailed physiological, cognitive and psychosocial functional measurements will be provided to test the conceptual framework postulated in Figure 8-5. Opportunities may also exist to learn from outliers of children who perform well despite low socioeconomic status and other adversities.

Novel interventions from future work in the SHINE cohort

Given the strong signals from early-life growth, HIV exposure and stunting, understanding these processes within birth cohorts such as the SHINE cohort may help to provide better interventions that work along multiple mechanisms. For example, a recent trial in Bangladesh showed microbiota-directed food supplements reduced systemic inflammation and improved growth[476]. Diet may also reduce chronic inflammation related to obesity[477]. Beyond diet, exercise interventions in children may work beyond improving cardiorespiratory fitness to also reduce inflammation[478]. Novel therapies could include antibiotics such as cotrimoxazole that reduce inflammation by both altering the microbiome and reducing immune activation[479]. Further insight may be obtained by measuring the complex signals between serum adipokines, growth factors and cytokines[480]. Future interventions could include anti-inflammatories, but mechanistic understanding may provide additional ways to mitigate the underlying drivers of inflammation. Beyond inflammation, a wider understanding of the processes behind faltering child growth and development is required that includes the HPA axis, infection, microbiome and their effects on child growth and physiology (Figure 8-5). This may inform the underlying risks for non- communicable diseases, as well as providing better interventions.

Success stories from nations that have reduced stunting

For certain nations, there are success stories at the policy level in reducing stunting, such as in Nepal, Ethiopia, Peru, Kyrgyz Republic and Senegal[83]. Although highly context-specific, approximately 40% of reduction in stunting was attributed to nutrition-specific strategies including health and nutrition[83]; 50% were attributed to nutrition-sensitive interventions including those focused on maternal education, maternal nutrition, maternal and newborn care, and family planning that reduced overall fertility and increased intervals between pregnancies[83].

Figure 8-6 Country wide roadmap to decreasing stunting at scale

Potential roadmap to decreasing stunting at scale from examining successful trajectories so far in Nepal, Ethiopia, Peru, Kyrgyz Republic and Senegal from[83]. NG: nongovernmental organisation, WASH: water, sanitation and hygiene

These national case studies showed that what worked was predominantly focused on maternal health, nutrition, education and gender, combined with improved living conditions[83]. A longer time course may also be required: Brazil achieved a dramatic reduction over 30 years by sustained action to improve child health, food security WASH and social protection in combination with water and sanitation[481]. To achieve greater catch-up in function in both growth and function, further sectors need to be included in national policy (Figure 8-7).

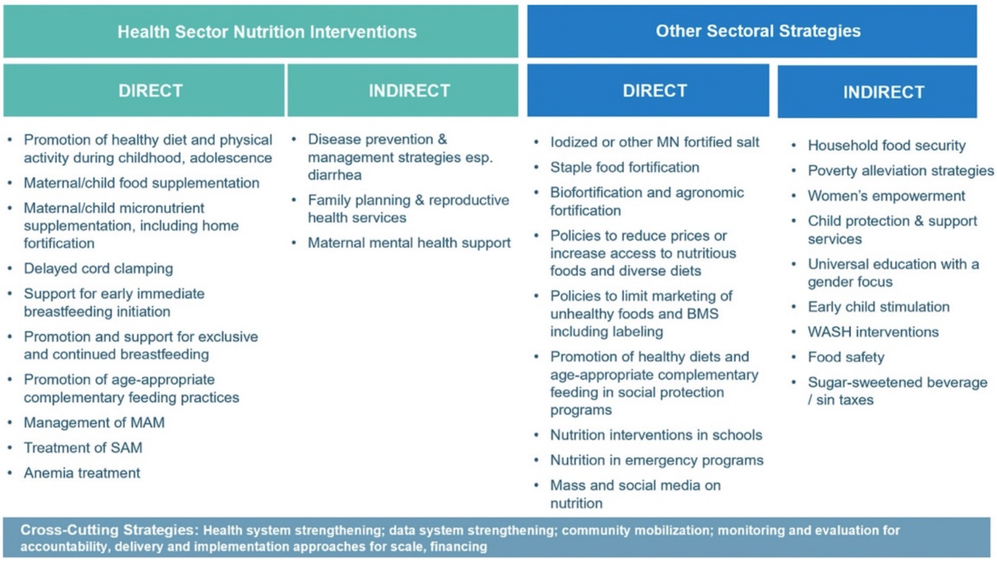


Figure 8-7 Broader interventions at a national level to reduce stunting

Broader interventions required at a national level for optimising child growth and development, from[83]. BMS: Breastmilk substitutes, MAM: moderate acute malnutrition, MN: micronutrient, SAM: severe acute malnutrition, WASH: water, sanitation and hygiene

Whilst these provide promising directions for national policy, they may take decades to have a sizeable effect and do not yet provide a treatment for the 250 million children currently at risk of poor development[1], 148 million children with stunting[3] or adults with increased risk of chronic disease. Therefore it is still crucial to understand the mechanisms underlying poor growth and function (Figure 8-5) to both develop better interventions and mitigate the previous effects of stunting. It is likely that early-life interventions such as SHINE need to achieve a greater size of effect for their benefits to be maintained, along with earlier, longer, broader and deeper interventions.

8.6 Conclusion

The SHINE Follow-up cohort has generated contemporary evidence of the ongoing importance of early-life growth and conditions for school-age growth and function.

This includes the long-term effects on cognition, cardiovascular fitness and head circumference for children born HIV-free. Contemporary growth and environmental factors also continue to shape school-age health and function.

The SHINE early-life nutrition and WASH interventions had minimal impact on school-age growth and function, with a possible slight improvement in handgrip strength observed in boys only. Interventions likely need to be earlier, longer, deeper and broader to be effective in improving long-term cognitive and physical function, which ultimately shape human capital across the life course. Understanding the complex interplay of psychosocial, inflammatory, microbiome, nutrition and nurturing factors is key to designing more comprehensive interventions that provide the size of benefit in growth and function required. In addition, adopting a life course approach to interventions as well as outcomes may have a dramatic impact on NCDs by using approaches that address environmental, nurturing and child factors that affect long-term growth and development[15]. Therefore understanding and then exploiting developmental plasticity may sustainably improve physiological capacity to optimise health, function and prevent chronic disease[15]. Generating the evidence for this, combined with the political will (as demonstrated by nations with successful reductions in stunting) may truly enable children to thrive as well as survive.

9 Appendices

9.1 Chapter 3 Appendix

A3-1 individual tools within the SAHARAN toolbox

1.3 Individual tools used within the SAHARAN toolbox from[192]

Domain	Sub-domain	Tool	Measurement(s)	Validity	Reliability	Responsiveness
Cognitive Function	Cognitive Processing	Kaufmann Assessment Battery for Children (KABC-II)	KABC-II measures across four domains of sequential, planning, learning and simultaneous scales. 8 core subtests can be combined as the mental processing index (MPI) to provide a global measure	The KABC-II was originally developed and validated using a large sample in the USA[198]. It has since been widely used across Africa[188], demonstrating robust factor analysis in Uganda[196] and psychometric validity in rural South Africa[190]). The KABC-II group of cognitive tests show less bias to school exposure in low-income settings [190]. Minor adaptations to the KABC-II required for this rural Zimbabwe population have been described elsewhere[238].	Reliability has been demonstrated in USA[198] and South Africa[239]. Recently, the QualiND model has demonstrated improved KABC-II monitoring and quality assurance using regular video review[194] across multiple countries and languages in Africa, including with a Shona translation in Zimbabwe[194]	Using KABC-II, a significant effect on cognition was detected with a nutrition intervention in South African children aged 6-11 years on two of the subtests[482] whilst in Ethiopia, 5 year olds with poorer growth also had worse KABC-II scores[483]. HIV positive children performed significantly worse than HIV-negative children in South Africa, Zimbabwe, Malawi and Uganda [127]. Similarly in separate studies in Burkina Faso, both stunted children [201] and those exposed to alcohol in pregnancy[201] performed significantly worse on KABC-II subtests.
Cognitive Function	Executive Function	Plus EF[1]	Inhibitory control: Hearts and Flowers (H&F)(note adapted to be stars and flowers for use in Africa) Inhibit interference: MSIT	The *PLUS-EF* tablet-based executive function tool, is an open-source android-based cognitive assessment tool that has been validated for school-aged children[166]. It has been adapted for use in the *PLUS -EF* tablet tests in urban Kenya[206]. It measures executive function including cognitive flexibility and inhibition using different tasks, of which 3 were used: Multi-source interference test, stars and flowers and flanker test. These tasks have been adapted for use in the *PLUS -EF* tablet tests in Kenya	Each individual test has shown reliability for an individual assessment situation, with quoted Cronbach alpha of MSIT 0.91 and H&F 0.81 [166]. A separate analysis of the Flanker task has shown good test-retest reliability and internal consistency, with Cronbach alpha >0.8[486].	MSIT performance has been shown to improve with age and brain function mapped using functional MRI[487]. The MSIT has also previously demonstrated an effect of socioeconomic status, subjective social status and perceived stress on children's executive function[488]. Hearts and Flowers has previously shown detrimental effects of moving home and

1

Domain	Sub-domain	Tool	Measurement(s)	Validity	Reliability	Responsiveness
			The flanker task requires (spatial) selective attention and executive control.	after extensive piloting[206]. [Note this only got added later so data are not presented in this paper]. Similar tests have been widely used across childhood, although mainly in high-income settings[484]. The MSIT has been shown to reliably activate the cingulo-frontal-parietal (CFP) cognitive/attention network by functional MRI[485].		socioeconomic status[489] as well as positive impacts of schooling exposure with time[490]. The Flanker test has previously showed improved selective attention with age in 4 to 6 year olds[491] and its inhibitory control is closely associated with school readiness[492].
Cognitive Function	Fine motor	Finger tapping	Time to perform sequential finger tapping	*The Rapid Sequential Continuous Movements* was a sensitive measure of fine motor skills that was associated with stunting in children in Jamaica[173].	During development, test-retest reliability was >0.78 and inter-observer agreements were above 0.96[205].	An impact of stunting was shown, as well as strong associations with a schooling achievement test and intelligence quotient (IQ)[205].
Cognitive Function	Academic function	School achievement test	Numeracy, literacy, Writing ability	Numeracy was assessed using elements from the Early Grade Maths Assessment[159] and UNICEF Multi-Indicator Cluster Survey (MICS) Foundational Learning Module[231], which had been widely applied across Zimbabwe. Literacy was assessed using reading elements from *The Early Grade Reading Assessment (EGRA),* which has been widely used across Africa to assess literacy[159]. Name writing ability has been shown to associated with emergent literacy skills[160].	EGMA report reliability with Spearman's rho of above 0.94 for number identification, discrimination and missing number subtests, with Cronbach alpha of 0.94, 0.82 and 0.58 respectively[163]. MICS used very similar questions with strong inter-rate reliability and agreement with EGRA and EGMA tests[204]. EGRA report reliability in Liberia of the 3 main elements used: letter identification, familiar word reading and non-word reading had Cronbach Alpha values of 0.78, 0.74 and 0.80 respectively[493].	EGRA has been previously used to assess individual levels of literacy in Kenya[494]. EGRA has been used to monitor also early grade reading interventions[203]. The overall structure of the test, has been similarly piloted in Bangladesh and is being used to assess children followed up in the WASH Benefits trial [78] (Tofail, personal communication).
	Socioemotional function	Strengths and Difficulties Questionnaire	Total difficulties score	*The Strengths and Difficulties Questionnaire (SDQ)* is a brief screening caregiver questionnaire for child mental health and behavioural problems from age 3-16 years. Both parent and teacher version have been shown to have construct and prediction validity in Holland[495]. It has been widely used in Africa[172] and found to be highly acceptable and applicable in sub-Saharan African settings [496].	Parent-reported total difficulties scores gave a Cronbach alpha of >0.77 in a large sample in Holland, although sub-scores were lower (0.42 to 0.8) [495].	This tool recently demonstrated the impact of LNS in similar aged children in Ghana[106].

Domain	Sub-domain	Tool	Measurement(s)	Validity	Reliability	Responsiveness
Cognitive Function	Sensory and overall function	WG UNICEF child functioning module (CFM)	Overall score	This tool was developed across multiple countries by UNICEF with extensive pretesting, cognitive interviewing and adaption[497,498].	The child functioning module was successfully performed in Mexico, Samoa and Serbia. It provided consistent prevalence rates similar to other tools using cut-offs describing 'a lot of difficulty' in functional domains or 'daily' levels of anxiety[209].	The CFM has also been previously used in the SHINE cohort at age 2 years and demonstrated good agreement in comparison with functional screening using the Malawi Development Assessment Tool (MDAT) [210,499].
Growth	Body composition	Bioimpedance	Impedance index (relative lean mass) Lean mass index, Phase angle	*Bioimpedance (BIA)* measures tissue health and the proportion of lean mass using an imperceptible electrical signal between the hand and foot[500]. This has been widely used globally to assess malnutrition[38], and the technique has been validated and calibration equations derived using other body composition techniques such as deuterium dilution[212] in the Gambia.		Bioimpedance has been used to show accretion of lean mass in children recovering from severe acute malnutrition (SAM)[38]. It has also been previously used in the SHINE study and showed a reduction with stunting (unpublished data). Lean mass correlates with organ size [34], improved neurodevelopment [35] and reduced metabolic risk[36]. An Ethiopian birth cohort study showed an association between lean mass at birth and socio-emotional function measured using the SDQ[186].
Growth	Body composition	Skinfold thickness		*Skinfold thickness* measures the subcutaneous fat layer around the body and describes its distribution. Triceps and maximal calf skinfold thicknesses give a measure of peripheral fat, whilst subscapular skinfolds measure central fat.	Acceptable inter-observer agreement using technical error of measurement was <1mm, within the ChroSAM study[242].	Fat mass provides short-term benefits for survival [30], but has longer-term metabolic health costs. Skinfold thickness and its distribution is a useful measure that reflects child malnutrition[38] and also as a marker for chronic disease risk[501]. They have also been previously used in the SHINE study and showed a reduction with stunting and HIV-exposure (unpublished data).
Growth	Anthropometry		Height, Weight, Head circumference, Waist circumference, Hip circumference, Mid-upper arm circumference, Calf circumference,	*2d) Anthropometry*: Height and weight provide body mass index (BMI) which is an important marker of metabolic health[501], together with waist circumference[502]. Head circumference is a reliable measure of brain growth and previous nutritional deprivation, and is highly correlated with neurodevelopment[286]. Calf circumference and mid-upper arm circumference are complementary to skinfold thicknesses in providing insights into the quality of growth[222].	Intra-observer technical error of measurement varied between 1 to 7 mm in the ChroSAM study[242].	
Growth	Knee-heel length		Knee-heel length	*Knee-heel (tibial) length* is a more sensitive measure of poor growth than leg length or stature and hence may be disproportionately reduced in stunting[273].		There is emerging evidence that knee-heel length is a proxy for organ size, e.g. kidney in stunted children [151]. It has also been previously used in the SHINE study and showed a reduction

Domain	Sub-domain	Tool	Measurement(s)	Validity	Reliability	Responsiveness
						with stunting and HIV-exposure (unpublished data).
Physical function	Strength	Handgrip strength	Average Handgrip strength	Handgrip strength is one of the core tests both within the ALPHA[178] and PREFIT[180] test batteries. This has been selected from a systematic review of the literature,[181] combined with what had been previously piloted in Malawi (Kerac, personal communication).	Previous studies had shown high reliability coefficients=0.97 and 0.98 for right and left hands, respectively, and no difference between test and retest[178,216].	*Handgrip strength* can be reduced in stunting[25] and in long-term assessments after acute malnutrition[222].
Physical function	Strength	Broad jump	Distance jumped	Broad jump is one of the core tests both within the ALPHA[178] and PREFIT[180] test batteries. This was similarly recommended from systematic review of the literature,[181] as a validated test of core muscular fitness[503]. It had been previously piloted in Malawi (Kerac, personal communication).	The broad jump has demonstrated good criterion validity and reliability. It had the strongest association with a range of both lower body muscular strength tests (eg vertical jump, squat jump and countermovement jump) and upper body strength tests (throw basketball, push ups and isometric strength)[503].	*The broad jump* is a measure of truncal tone and fitness[25] and has been shown to be reduced in stunted children in South Africa[504].
Physical function	Cardiovascular fitness	Shuttle Run Test	Level reached	*The 20 meter shuttle run test (SRT)* is used to measure physical and aerobic capacity[505]. It has been shown to have good criterion related validity for cardiorespiratory fitness in both adults and children[506]. The criterion validity of the 20 m shuttle run test has been shown to be superior to similar measures of cardiovascular fitness such as the mile walk/run test[178,507].	Reliability has been stated to be acceptable with no systematic bias[178,507].	Stunting was a strong predictor of decreased fitness in the beep test when applied in Kenya[219]
Blood Pressure				BP can be increased in stunting, particularly in combination with overweight[315].		BP in 8 year-olds in Nepal was independently negatively associated with leg and kidney length[34], and is a marker of homeostatic reserve and later cardio-metabolic risk[316].

Table A1 9-1 Supplementary Table S1: Individual tools used within the SAHARAN toolbox.

Measures, validity, reliability and responsiveness are based on previous literature. Validity is defined as how applicable the tool is in measuring a functional construct. This includes face validity (how it looks to the population), cross-cultural validity, content validity (how it measures), construct and structural validity (if measures are based on consistent hypotheses and reflect appropriate functional domains) from[192].

A3-2 List of experts who provided advice on measurement tools

A range of experts were contacted to provide additional and contemporary input on tool selection, applicability and validity. These included:

1) ***Melissa Gladstone** (Professor in Neurodevelopmental Paediatrics and International Child Health at the University of Liverpool). She developed the MDAT scale and is a collaborator on this project
2) **Amina Abubakar** (Professor of Psychology and Public Health at Pwani University, Kenya). She developed the Kilifi Development Inventory and has employed a range of cognitive measurement techniques across Africa.
3) **Natasha Lelijveld** (research fellow at Southampton University). She performed a similar broad test battery for survivors of Chronic malnutrition in Malawi in the ChroSAM study[94].
4) **Patricia Kariger**, (Assistant professor in developmental psychology based at University of Berkeley)[14]. She worked on WASH Benefits team[72] and is developing the PLUS -EF tablet tests in urban Kenya[206]
5) **Tamsen Rochat** (assistant professor in psychology at University of Witswatersrand, South Africa). psychologist with extensive experience of measuring school-aged cognitive function and contributing factors within South Africa (both peri-urban and rural).
6) **Elizabeth Prado**, (psychologist and assistant Professor at UC Davis, USA). She is author of numerous reviews[14] and was lead investigator on ILINS-DYAD study in Ghana[95]

7) **Jaya Chandna**, (psychologist at London School of Hygiene and Tropical Medicine (LSHTM)) who previously performed neurodevelopmental assessment in the SHINE trial at 2 years[77] and has experience with multiple child neurodevelopmental tools.
8) **Joanie Mitchell**, (clinical psychologist) who has extensively using KABC-II tool in rural South Africa[190]
9) **David Bearden** (Assistant Professor in paediatric neurology, University of Rochester, USA) Co-Investigators on the HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study
10) **Heather Adams** (University of Rochester, USA), Co-Investigators on the HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study
11) *** Megan McHenry** (Professor of pediatrics, University of Indiana),
12) ***Supriya Bhavnani** (team lead for Developmental Assessment on an E-Platform (DEEP), MIT, USA)
13) ***Debarati Mukherjee** (faculty fellow at Indian Institute of Public Health, Indian lead for DEEP)
14) **Jelena Obradovic** (Associate Professor, Psychology, Stanford), who has extensive experience and was one of the developers of the PLUS-EF tool

<u>For physical function</u>

15) **Marko Kerac**, (Associate Professor, Public Health Nutrition, LSHTM). Previous supervision of piloting physical function measurements in Malawi.

16) **Keith Brazendale** (Assistant Professor, Department of Health Sciences, University of Central Florida). Use of fitbits and polar heart rate monitors for detailed measurement of physical function in children.

For growth and body composition:

17) **Jonathan Wells** (Professor of Anthropology and Paediatric Nutrition, UCL GOS Institute of Child Health)
18) **Carlos Eternod-Grijalva** (research Fellow in nutrition and child development, LSHTM)
19) **Suneetha Kadiyala** (Director of IMMANA, Professor of Global Nutrition, LSHTM)

*The selection of tools led to these colleagues collaborating on a review "**The current landscape and future of tablet-based cognitive assessments for children in low-resourced settings".** *Draft shortly to be submitted to 'Child Development Perspectives'*

9.2 Chapter 4 Appendix

A4-1 Child sex supplementary table

Domain	Other variables	female N1	Mean (SD)	Male N2	Mean (SD)	p-value:
Child	Mean child age / years (SD)	506	7.3 (0.2)	484	7.3 (0.2)	0.34
	Mean Height / Kg (SD)	506	120.2 (4.9)	484	120.1 (4.9)	0.80
	Mean Weight /Kg (SD)	505	21.4 (3.0)	484	21.6 (2.6)	0.36
Socioeconomic	Mean Socioeconomic status (SD)	498	1.6 (0.6)	476	1.6 (0.6)	0.44
	Mean Household Food Insecurity Assessment Scale (SD)	505	12 (4)	484	12 (4)	0.9
	Mean Household Dietary Diversity Scale (SD)	505	8 (2)	484	8 (2)	0.73
	Mean Household Water Insecurity Experiences Scale (SD)	505	12 (1)	484	12 (1)	0.73
	Number of Female headed households	505	116	484	102	0.65
	Mean adversity score (SD)	497	2 (2)	477	2 (1)	0.47
	Mean Total schooling / year (SD)	496	3 (1)	472	3 (1)	0.86
	Median Number of books at home (IQR)	505	0 (0,1)	484	0 (0,1)	0.07
Maternal	Mean depression score (SD)	505	3 (5)	484	3 (4)	0.27
	Mean social support score (SD)	505	4 (0)	483	4 (0)	0.07
	Mean gender norm score (SD)	505	4 (1)	484	4 (1)	0.7
	Mean breastfed time / months (SD)	479	19 (4)	463	19 (4)	0.65
Nurture	Mean discipline score (SD)	505	2 (2)	484	2 (2)	0.87
	Mean child parent relationship score (SD)	503	3 (1)	484	3 (1)	0.28

Table A4-1 Contemporary environmental factors split by child sex

A4-2 Household adversity scores split by child sex

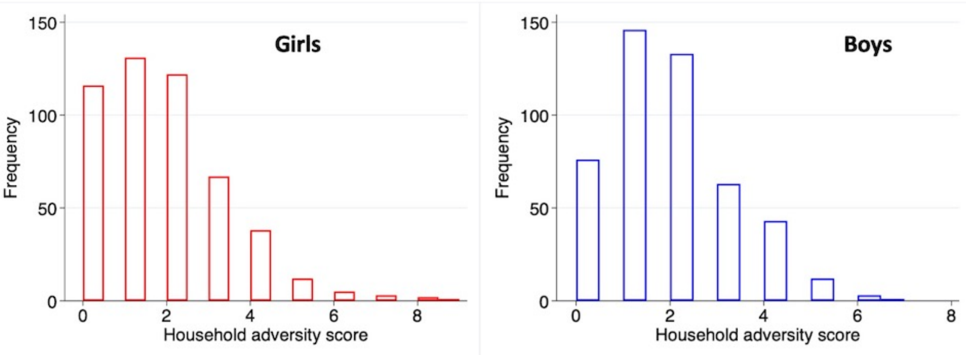


Figure A4-1 Household adversity

Household adversity scores in the SHINE cohort for children born to mothers without HIV split by child sex

A4-2 Associations of 7 year growth with cognitive function

Growth Exposures	Outcome	n	GEE model						
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	n in adjusted models	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	MPI	990	1.51 (0.67, 2.35)	1.55 (0.71, 2.39)	1.58 (0.8, 2.36)	980	1.3 (0.5, 2.1)	0.12	0.12
WAZ	MPI	988	1.66 (0.88, 2.45)	1.68 (0.9, 2.47)	1.69 (0.93, 2.46)	978	1.33 (0.55, 2.11)	0.13	0.11
BMIZ	MPI	988	0.95 (0.11, 1.79)	0.94 (0.1, 1.77)	0.96 (0.16, 1.76)	978	0.66 (-0.14, 1.46)	0.07	0.04
Knee-heel length	MPI	989	0.42 (0.07, 0.76)	0.43 (0.09, 0.78)	0.62 (0.26, 0.97)	979	0.53 (0.17, 0.89)	0.07	0.11
Head circumference	MPI	990	0.87 (0.37, 1.38)	0.88 (0.37, 1.39)	1.23 (0.71, 1.76)	980	1.17 (0.63, 1.7)	0.12	0.15
MUAC	MPI	989	0.6 (0.05, 1.15)	0.61 (0.06, 1.16)	0.78 (0.25, 1.31)	979	0.55 (0.02, 1.09)	0.07	0.07
Waist circ	MPI	989	0.02 (-0.22, 0.26)	0.02 (-0.22, 0.26)	0.11 (-0.12, 0.33)	979	0.12 (-0.11, 0.34)	0.01	0.03
Hip circumference	MPI	990	0.43 (0.26, 0.6)	0.43 (0.27, 0.6)	0.42 (0.25, 0.59)	980	0.35 (0.18, 0.51)	0.15	0.13
Calf circumference	MPI	989	0.76 (0.36, 1.17)	0.77 (0.37, 1.17)	0.9 (0.49, 1.31)	979	0.79 (0.39, 1.19)	0.11	0.12
Lean mass index	MPI	982	-0.08 (-0.56, 0.41)	-0.06 (-0.55, 0.43)	0.23 (-0.3, 0.77)	972	0.11 (-0.44, 0.67)	-0.01	0.02
Impedance Index	MPI	982	1.89 (-0.58, 4.36)	1.99 (-0.5, 4.48)	4.25 (1.68, 6.83)	972	3.15 (0.4, 5.91)	0.04	0.08
Phase angle	MPI	982	0.21 (-1.07, 1.49)	0.19 (-1.09, 1.46)	0.23 (-1.01, 1.48)	972	0.33 (-0.94, 1.6)	0.01	0.03
Total Skinfold	MPI	987	0.16 (0.06, 0.26)	0.16 (0.06, 0.26)	0.15 (0.05, 0.26)	978	0.09 (-0.01, 0.19)	0.09	0.05

Peripheral Skinfold	MPI	988	0.32 (0.16, 0.48)	0.32 (0.15, 0.48)	0.25 (0.07, 0.42)	978	0.21 (0.03, 0.38)	0.11	0.06
Central Skinfold	MPI	989	0.27 (0, 0.54)	0.27 (0, 0.54)	0.37 (0.1, 0.63)	980	0.18 (-0.09, 0.44)	0.07	0.05
Hb	MPI	990	0.32 (-0.32, 0.96)	0.31 (-0.33, 0.95)	0.12 (-0.52, 0.77)	980	0.22 (-0.41, 0.84)	0.03	0.02

Table A4-2 Association of SAHARAN growth variables with mental processing index (MPI).

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Growth Exposure x16	Outcome	n	GEE Mean difference (95% CI)				Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
			Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).		
HAZ	SAT	990	4.54 (2.51, 6.57)	4.57 (2.57, 6.57)	4.15 (2.31, 5.99)	3.52 (1.68, 5.36)	0.15	0.13
WAZ	SAT	988	4.25 (2.14, 6.36)	4.23 (2.14, 6.31)	3.85 (1.93, 5.76)	3.17 (1.27, 5.06)	0.13	0.1
BMIZ	SAT	988	1.77 (-0.4, 3.94)	1.71 (-0.45, 3.87)	1.6 (-0.49, 3.69)	1.18 (-0.87, 3.23)	0.05	0.03
Knee-heel length	SAT	989	2.15 (1.3, 3)	2.16 (1.33, 3)	1.68 (0.82, 2.54)	1.49 (0.63, 2.35)	0.15	0.12
Head circumference	SAT	990	1.34 (0.16, 2.52)	1.34 (0.16, 2.53)	2.54 (1.26, 3.82)	2.23 (0.94, 3.51)	0.07	0.11
MUAC	SAT	989	2.57 (1.32, 3.83)	2.58 (1.33, 3.83)	2.06 (0.85, 3.28)	1.49 (0.31, 2.66)	0.12	0.08
Waist circumference	SAT	989	0.22 (-0.41, 0.85)	0.21 (-0.42, 0.83)	0.16 (-0.4, 0.72)	0.24 (-0.31, 0.78)	0.03	0.03
Hip circumference	SAT	990	1.32 (0.89, 1.76)	1.32 (0.88, 1.75)	1.1 (0.63, 1.57)	0.91 (0.45, 1.36)	0.19	0.14
Calf circumference	SAT	989	2.18 (1.15, 3.21)	2.18 (1.15, 3.22)	1.9 (0.95, 2.85)	1.58 (0.64, 2.51)	0.13	0.11
Lean mass index	SAT	982	-1.17 (-2.55, 0.2)	-1.15 (-2.53, 0.23)	-0.11 (-1.59, 1.37)	-0.17 (-1.65, 1.3)	-0.06	0
Impedance Index	SAT	982	6.12 (-0.57, 12.82)	6.23 (-0.47, 12.94)	9.24 (2.79, 15.7)	7.27 (0.61, 13.92)	0.06	0.07
Phase angle	SAT	982	1.8 (-1.19, 4.79)	1.78 (-1.2, 4.76)	2.56 (-0.45, 5.56)	2.91 (-0.1, 5.92)	0.04	0.07
Total Skinfold	SAT	987	0.57 (0.33, 0.82)	0.57 (0.32, 0.81)	0.37 (0.12, 0.61)	0.22 (-0.02, 0.46)	0.13	0.04
Peripheral Skinfold	SAT	988	1.06 (0.64, 1.49)	1.05 (0.63, 1.47)	0.66 (0.22, 1.09)	0.49 (0.05, 0.94)	0.14	0.06
Central Skinfold	SAT	989	0.92 (0.43, 1.4)	0.91 (0.43, 1.4)	0.71 (0.21, 1.2)	0.38 (-0.1, 0.86)	0.1	0.04

Hb	SAT	990	0.3 (-1.11, 1.72)	0.3 (-1.11, 1.72)	0.37 (-0.98, 1.71)	0.46 (-0.84, 1.76)	0.01	0.01

Table A4-3 Association of SAHARAN growth variables with the School Achievement Test (SAT)

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Growth Exposure	Outcome		GEE Mean difference (95% CI)					
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	PlusEF	978	1.79 (-0.03, 3.62)	1.79 (-0.04, 3.62)	1.54 (-0.28, 3.36)	1.56 (-0.06, 3.18)	0.07	0.06
WAZ	PlusEF	976	2.66 (0.84, 4.48)	2.67 (0.84, 4.5)	2.22 (0.36, 4.07)	2.18 (0.53, 3.83)	0.09	0.08
BMIZ	PlusEF	976	2.08 (0.25, 3.92)	2.09 (0.25, 3.93)	1.66 (-0.23, 3.55)	1.55 (-0.23, 3.33)	0.07	0.05
Knee-heel length	PlusEF	977	1 (0.21, 1.78)	1 (0.21, 1.79)	0.61 (-0.2, 1.42)	0.66 (-0.07, 1.4)	0.08	0.06
Head circumference	PlusEF	978	2.15 (1.1, 3.19)	2.11 (1.07, 3.15)	2.06 (0.97, 3.15)	2.27 (1.2, 3.33)	0.13	0.14
MUAC	PlusEF	977	1.94 (0.82, 3.07)	1.93 (0.82, 3.05)	1.44 (0.34, 2.55)	1.5 (0.43, 2.56)	0.1	0.09
Waist circumference	PlusEF	977	0.44 (-0.1, 0.98)	0.44 (-0.11, 0.98)	0.17 (-0.39, 0.72)	0.38 (-0.16, 0.92)	0.06	0.05
Hip circumference	PlusEF	978	0.78 (0.42, 1.14)	0.78 (0.42, 1.13)	0.66 (0.26, 1.06)	0.54 (0.18, 0.91)	0.13	0.09
Calf circumference	PlusEF	977	1.3 (0.46, 2.14)	1.29 (0.44, 2.13)	0.98 (0.15, 1.8)	1.06 (0.3, 1.82)	0.09	0.07
Lean mass index	PlusEF	970	0.12 (-1.05, 1.29)	0.12 (-1.05, 1.3)	0.83 (-0.43, 2.09)	1.24 (0.09, 2.39)	0.01	0.06
Impedance Index	PlusEF	970	5.32 (-0.21, 10.85)	5.34 (-0.2, 10.88)	6.27 (0.57, 11.96)	7.51 (2.18, 12.83)	0.06	0.08
Phase angle	PlusEF	970	0.41 (-2.33, 3.14)	0.38 (-2.33, 3.09)	0.29 (-2.25, 2.84)	0.41 (-2.3, 3.11)	0.01	0.01

Total Skinfold	PlusEF	975	0.32 (0.09, 0.56)	0.32 (0.09, 0.56)	0.32 (0.07, 0.57)	0.16 (-0.09, 0.4)	0.08	0.04
Peripheral Skinfold	PlusEF	976	0.63 (0.26, 1)	0.62 (0.25, 0.99)	0.53 (0.14, 0.92)	0.4 (0.02, 0.77)	0.09	0.06
Central Skinfold	PlusEF	977	0.48 (0.01, 0.94)	0.49 (0.02, 0.95)	0.56 (0.07, 1.06)	0.14 (-0.34, 0.63)	0.06	0.02
Hb	PlusEF	978	0.06 (-1.18, 1.31)	0.06 (-1.18, 1.3)	0.16 (-1, 1.32)	0.5 (-0.63, 1.64)	0	0.02

Table A4-4 Association of SAHARAN growth variables with the Plus EF toolbox, (tablet-based measure of executive function).

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children’s books at home, caregiver education and gender norms

Growth Exposure x16	Outcome		GEE Mean difference (95% CI)						
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	n in adjusted models	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Fine motor	986	-0.86 (-1.4, -0.32)	-0.89 (-1.42, -0.36)	-0.74 (-1.23, -0.25)	976	-0.63 (-1.1, -0.17)	-0.12	-0.1
WAZ	Fine motor	984	-1.05 (-1.57, -0.52)	-1.05 (-1.57, -0.54)	-1.02 (-1.51, -0.53)	974	-0.9 (-1.38, -0.42)	-0.14	-0.12
BMIZ	Fine motor	984	-0.7 (-1.22, -0.17)	-0.68 (-1.22, -0.15)	-0.8 (-1.31, -0.29)	974	-0.71 (-1.22, -0.2)	-0.09	-0.08
Knee-heel length	Fine motor	985	-0.32 (-0.56, -0.08)	-0.33 (-0.57, -0.1)	-0.28 (-0.51, -0.05)	975	-0.26 (-0.48, -0.04)	-0.09	-0.09
Head circumference	Fine motor	986	-0.35 (-0.67, -0.03)	-0.36 (-0.68, -0.05)	-0.61 (-0.92, -0.31)	976	-0.59 (-0.91, -0.27)	-0.08	-0.14
MUAC	Fine motor	985	-0.64 (-0.95, -0.32)	-0.64 (-0.95, -0.33)	-0.62 (-0.93, -0.31)	975	-0.56 (-0.87, -0.26)	-0.13	-0.12
Waist circumference	Fine motor	985	-0.07 (-0.21, 0.07)	-0.07 (-0.21, 0.07)	-0.09 (-0.23, 0.05)	975	-0.11 (-0.25, 0.03)	-0.03	-0.05
Hip circumference	Fine motor	986	-0.27 (-0.37, -0.17)	-0.27 (-0.37, -0.17)	-0.25 (-0.35, -0.15)	976	-0.21 (-0.32, -0.11)	-0.16	-0.14
Calf circumference	Fine motor	985	-0.55 (-0.8, -0.31)	-0.56 (-0.8, -0.32)	-0.53 (-0.76, -0.31)	975	-0.5 (-0.73, -0.28)	-0.14	-0.12
Lean mass index	Fine motor	978	-0.19 (-0.56, 0.19)	-0.19 (-0.56, 0.18)	-0.56 (-0.98, -0.13)	968	-0.55 (-0.97, -0.13)	-0.04	-0.1
Impedance Index	Fine motor	978	-2.28 (-4.12, -0.45)	-2.33 (-4.15, -0.52)	-3.49 (-5.44, -1.54)	968	-3.18 (-5.14, -1.22)	-0.09	-0.13
Phase angle	Fine motor	978	-0.05 (-0.65, 0.55)	-0.05 (-0.66, 0.56)	-0.35 (-0.97, 0.27)	968	-0.4 (-1.02, 0.23)	0	-0.03
Total Skinfold	Fine motor	983	-0.15 (-0.22, -0.09)	-0.15 (-0.22, -0.09)	-0.12 (-0.19, -0.06)	974	-0.09 (-0.16, -0.03)	-0.14	-0.09

Peripheral Skinfold	Fine motor	984	-0.28 (-0.38, -0.18)	-0.28 (-0.38, -0.18)	-0.21 (-0.31, -0.1)	974	-0.19 (-0.3, -0.08)	-0.16	-0.11
Central Skinfold	Fine motor	985	-0.22 (-0.35, -0.09)	-0.22 (-0.34, -0.09)	-0.21 (-0.33, -0.08)	976	-0.13 (-0.24, -0.01)	-0.1	-0.06
Hb	Fine motor	986	-0.09 (-0.41, 0.23)	-0.09 (-0.41, 0.23)	-0.03 (-0.33, 0.27)	976	-0.09 (-0.38, 0.2)	-0.02	-0.01

Table A4-5 Association of SAHARAN growth variables with fastest fine motor speed in seconds to complete the finger tapping task.

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms.

Growth Exposure x16	Outcome		GEE Mean difference (95% CI)						
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	n in adjusted models	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	SDQ	989	0.02 (-0.36, 0.39)	0.05 (-0.33, 0.42)	0.11 (-0.26, 0.49)	979	0.18 (-0.19, 0.56)	0.01	0.01
WAZ	SDQ	987	-0.05 (-0.42, 0.31)	-0.04 (-0.41, 0.33)	0.05 (-0.32, 0.41)	977	0.07 (-0.31, 0.45)	0.02	0.01
BMIZ	SDQ	987	-0.12 (-0.44, 0.21)	-0.13 (-0.46, 0.19)	-0.07 (-0.4, 0.25)	977	-0.1 (-0.41, 0.22)	0.02	-0.01
Knee-heel length	SDQ	988	0.03 (-0.13, 0.2)	0.05 (-0.12, 0.21)	0.07 (-0.09, 0.23)	978	0.1 (-0.06, 0.27)	0.01	0.02
Head circumference	SDQ	989	-0.04 (-0.27, 0.19)	-0.04 (-0.27, 0.2)	-0.17 (-0.42, 0.08)	979	-0.1 (-0.35, 0.16)	-0.01	-0.05
MUAC	SDQ	988	-0.18 (-0.4, 0.03)	-0.17 (-0.39, 0.04)	-0.13 (-0.36, 0.09)	978	-0.11 (-0.33, 0.12)	-0.01	-0.04
Waist circumference	SDQ	988	0.01 (-0.1, 0.11)	0 (-0.1, 0.11)	0.01 (-0.1, 0.12)	978	0.01 (-0.1, 0.12)	0.02	0
Hip circumference	SDQ	989	-0.05 (-0.12, 0.03)	-0.05 (-0.12, 0.02)	-0.03 (-0.11, 0.04)	979	-0.02 (-0.09, 0.06)	-0.01	-0.02
Calf circumference	SDQ	988	-0.05 (-0.21, 0.12)	-0.04 (-0.21, 0.12)	-0.02 (-0.19, 0.15)	978	0 (-0.17, 0.17)	0.01	-0.01
Lean mass index	SDQ	981	0.15 (-0.1, 0.4)	0.16 (-0.09, 0.41)	0.12 (-0.16, 0.41)	971	0.09 (-0.18, 0.36)	0.04	0.02
Impedance Index	SDQ	981	0.63 (-0.58, 1.83)	0.73 (-0.5, 1.95)	0.58 (-0.72, 1.88)	971	0.67 (-0.62, 1.96)	0.03	0.03
Phase angle	SDQ	981	0.35 (-0.17, 0.88)	0.34 (-0.18, 0.86)	0.34 (-0.2, 0.88)	971	0.27 (-0.28, 0.81)	0.03	0.02
Total Skinfold	SDQ	986	-0.06 (-0.11, -0.01)	-0.06 (-0.11, -0.01)	-0.05 (-0.1, 0)	977	-0.03 (-0.08, 0.02)	-0.05	-0.05
Peripheral Skinfold	SDQ	987	-0.11 (-0.18, -0.03)	-0.11 (-0.19, -0.03)	-0.08 (-0.16, 0)	977	-0.06 (-0.14, 0.01)	-0.06	-0.05
Central Skinfold	SDQ	988	-0.11 (-0.23, 0)	-0.11 (-0.22, 0)	-0.09 (-0.21, 0.04)	979	-0.05 (-0.16, 0.06)	-0.03	-0.03

Hb	SDQ	989	-0.14 (-0.42, 0.14)	-0.15 (-0.43, 0.13)	-0.16 (-0.46, 0.13)	979	-0.23 (-0.49, 0.04)	-0.03	-0.05

Table A4-6 Association of SAHARAN growth variables with the strengths and difficulties questionnaire (SDQ) where higher scores show worse socioemotional function.

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Growth Exposure x16	Outcome		GEE Mean difference (95% CI)						
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	n in adjusted models	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Child socioem	973	0.03 (-0.03, 0.09)	0.03 (-0.02, 0.09)	0.02 (-0.03, 0.07)	979	0.04 (-0.01, 0.09)	0.04	0.05
WAZ	Child socioem	971	0.03 (-0.02, 0.09)	0.04 (-0.02, 0.09)	0.03 (-0.03, 0.08)	977	0.04 (-0.01, 0.1)	0.04	0.05
BMIZ	Child socioem	971	0.02 (-0.03, 0.08)	0.02 (-0.03, 0.08)	0.02 (-0.04, 0.08)	977	0.03 (-0.02, 0.08)	0.03	0.03
Knee-heel length	Child socioem	972	0 (-0.03, 0.02)	0 (-0.02, 0.02)	0 (-0.02, 0.03)	978	0.01 (-0.01, 0.04)	0	0.04
Head circumference	Child socioem	973	0.05 (0.02, 0.08)	0.05 (0.02, 0.08)	0.04 (0.01, 0.07)	979	0.06 (0.02, 0.09)	0.1	0.07
MUAC	Child socioem	972	0 (-0.04, 0.03)	0 (-0.04, 0.03)	0 (-0.04, 0.03)	978	0 (-0.03, 0.04)	-0.01	0.01
Waist circumference	Child socioem	972	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)	978	0.02 (0, 0.03)	0.03	0.08
Hip circumference	Child socioem	973	0 (-0.01, 0.01)	0 (-0.01, 0.01)	0 (-0.01, 0.01)	979	0.01 (0, 0.02)	0.02	0.03
Calf circumference	Child socioem	972	0.01 (-0.01, 0.04)	0.01 (-0.01, 0.04)	0.01 (-0.02, 0.04)	978	0.02 (-0.01, 0.04)	0.03	0.06
Lean mass index	Child socioem	965	0.03 (-0.01, 0.06)	0.03 (-0.01, 0.06)	0.04 (0, 0.07)	971	0.05 (0.01, 0.09)	0.05	0.11
Impedance Index	Child socioem	965	0.13 (-0.06, 0.32)	0.13 (-0.06, 0.32)	0.17 (-0.02, 0.36)	971	0.24 (0.03, 0.45)	0.05	0.32
Phase angle	Child socioem	965	0.01 (-0.06, 0.08)	0.01 (-0.07, 0.08)	0.01 (-0.07, 0.08)	971	0.04 (-0.04, 0.11)	0.01	0.05
Total Skinfold	Child socioem	970	0 (-0.01, 0)	0 (-0.01, 0)	0 (-0.01, 0.01)	977	0 (-0.01, 0.01)	-0.04	-0.04
Peripheral Skinfold	Child socioem	971	0 (-0.02, 0.01)	0 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	977	0 (-0.02, 0.01)	-0.02	-0.03
Central Skinfold	Child socioem	972	-0.01 (-0.03, 0)	-0.01 (-0.03, 0)	0 (-0.02, 0.01)	979	-0.01 (-0.03, 0.01)	-0.06	-0.05

Hb	Child socioem	973	-0.01 (-0.05, 0.04)	-0.01 (-0.05, 0.04)	-0.02 (-0.06, 0.02)	979	0.04 (-0.01, 0.09)	-0.01	0

Table A4-7 Associations of SAHARAN growth variables with child socioemotional function (Child socioem)

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

A4-3 Associations of 7 year growth with physical functions

Growth Exposure x16	Outcome	n	GEE Mean difference (95% CI)					
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Grip strength	990	1.04 (0.92, 1.17)	1.04 (0.92, 1.16)	1.07 (0.95, 1.19)	1.08 (0.96, 1.2)	0.49	0.5
WAZ	Grip strength	988	1.13 (1, 1.26)	1.12 (1, 1.25)	1.15 (1.02, 1.28)	1.17 (1.05, 1.3)	0.51	0.53
BMIZ	Grip strength	988	0.67 (0.55, 0.8)	0.67 (0.54, 0.8)	0.67 (0.53, 0.8)	0.69 (0.56, 0.82)	0.3	0.3
Knee-heel length	Grip strength	989	0.48 (0.43, 0.54)	0.48 (0.42, 0.53)	0.48 (0.42, 0.54)	0.48 (0.42, 0.54)	0.48	0.49
Head circumference	Grip strength	990	0.35 (0.27, 0.44)	0.36 (0.27, 0.44)	0.28 (0.19, 0.36)	0.29 (0.21, 0.38)	0.28	0.23
MUAC	Grip strength	989	0.63 (0.54, 0.73)	0.63 (0.53, 0.72)	0.66 (0.56, 0.75)	0.66 (0.57, 0.75)	0.43	0.45
Waist circumference	Grip strength	989	0.26 (0.22, 0.29)	0.25 (0.22, 0.29)	0.23 (0.2, 0.27)	0.24 (0.21, 0.28)	0.42	0.39
Hip circumference	Grip strength	990	0.2 (0.17, 0.23)	0.2 (0.17, 0.23)	0.2 (0.17, 0.23)	0.21 (0.18, 0.24)	0.42	0.43
Calf circumference	Grip strength	989	0.47 (0.38, 0.56)	0.47 (0.38, 0.56)	0.47 (0.38, 0.56)	0.47 (0.38, 0.57)	0.41	0.42
Lean mass index	Grip strength	982	0.62 (0.54, 0.71)	0.62 (0.54, 0.7)	0.68 (0.59, 0.78)	0.7 (0.6, 0.79)	0.42	0.47

Impedance Index	Grip strength	982	4.48 (4.08, 4.88)	4.47 (4.07, 4.87)	4.7 (4.29, 5.11)	4.75 (4.33, 5.17)	0.59	0.63
Phase angle	Grip strength	982	1.03 (0.81, 1.24)	1.03 (0.82, 1.24)	4.7 (4.29, 5.11)	1.01 (0.81, 1.21)	0.3	0.29
Total Skinfold	Grip strength	987	0.03 (0, 0.05)	0.02 (0, 0.05)	0.04 (0.02, 0.06)	0.04 (0.02, 0.06)	0.08	0.12
Peripheral Skinfold	Grip strength	988	0.05 (0.01, 0.09)	0.04 (0.01, 0.08)	0.07 (0.03, 0.1)	0.07 (0.03, 0.1)	0.09	0.13
Central Skinfold	Grip strength	989	0.04 (0, 0.08)	0.04 (0, 0.08)	0.08 (0.05, 0.12)	0.06 (0.02, 0.1)	0.07	0.1
Hb	Grip strength	990	0.17 (0.07, 0.27)	0.17 (0.07, 0.27)	0.14 (0.04, 0.24)	0.16 (0.06, 0.26)	0.11	0.1

Table A4-8 Association of growth variables with grip strength

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Growth Exposure x16	Outcome	n	GEE Mean difference (95% CI) Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Broad jump	990	4.35 (3.28, 5.42)	4.38 (3.32, 5.44)	4.23 (3.24, 5.22)	4.27 (3.29, 5.24)	0.25	0.25
WAZ	Broad jump	988	3.14 (2.13, 4.15)	3.17 (2.17, 4.16)	3.26 (2.29, 4.22)	3.33 (2.38, 4.27)	0.17	0.19
BMIZ	Broad jump	988	0.51 (-0.45, 1.47)	0.52 (-0.43, 1.47)	0.74 (-0.27, 1.74)	0.82 (-0.16, 1.8)	0.03	0.04
Knee-heel length	Broad jump	989	2.02 (1.59, 2.45)	2.03 (1.6, 2.47)	1.81 (1.37, 2.26)	1.85 (1.4, 2.29)	0.25	0.24
Head circumference	Broad jump	990	0.68 (-0.02, 1.39)	0.69 (-0.01, 1.39)	0.48 (-0.21, 1.18)	0.5 (-0.22, 1.23)	0.07	0.05
MUAC	Broad jump	989	1.46 (0.67, 2.26)	1.47 (0.67, 2.27)	1.23 (0.5, 1.96)	1.23 (0.49, 1.96)	0.12	0.11
Waist circumference	Broad jump	989	0.42 (0.15, 0.69)	0.42 (0.15, 0.69)	0.33 (0.05, 0.61)	0.39 (0.12, 0.66)	0.08	0.08
Hip circumference	Broad jump	990	0.51 (0.28, 0.74)	0.52 (0.29, 0.75)	0.48 (0.24, 0.72)	0.45 (0.22, 0.69)	0.13	0.12
Calf circumference	Broad jump	989	1.38 (0.76, 1.99)	1.38 (0.77, 2)	1.14 (0.58, 1.7)	1.14 (0.57, 1.71)	0.15	0.12
Lean mass index	Broad jump	982	3.02 (2.35, 3.68)	3.02 (2.35, 3.69)	2.45 (1.67, 3.24)	2.58 (1.82, 3.34)	0.25	0.21
Impedance Index	Broad jump	982	20.16 (16.78, 23.54)	20.24 (16.86, 23.61)	17.42 (13.79, 21.05)	17.8 (14.3, 21.3)	0.33	0.30
Phase angle	Broad jump	982	3.97 (1.66, 6.27)	3.98 (1.68, 6.27)	3.93 (1.63, 6.24)	4.07 (1.74, 6.39)	0.14	0.15
Total Skinfold	Broad jump	987	-0.16 (-0.32, -0.01)	-0.16 (-0.32, 0)	-0.16 (-0.34, 0.02)	-0.21 (-0.38, -0.03)	-0.06	-0.08
Peripheral Skinfold	Broad jump	988	-0.24 (-0.5, 0.03)	-0.23 (-0.5, 0.04)	-0.25 (-0.54, 0.04)	-0.29 (-0.57, 0)	-0.06	-0.06
Central Skinfold	Broad jump	989	-0.34 (-0.67, -0.01)	-0.34 (-0.67, 0)	-0.31 (-0.68, 0.06)	-0.41 (-0.78, -0.04)	-0.07	-0.07

Hb	Broad jump	990	0.55 (-0.23, 1.34)	0.55 (-0.23, 1.34)	0.34 (-0.37, 1.05)	0.45 (-0.27, 1.16)	0.04	0.03

Table A4-9 Association of SAHARAN growth variables with broad jump

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Shuttle Run (VO2max)

Growth Exposure x16	Outcome	n	GEE Mean difference (95% CI) Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Shuttle run	990	0.18 (-0.06, 0.43)	0.19 (-0.05, 0.44)	0.17 (-0.07, 0.42)	0.19 (-0.06, 0.44)	0.06	0.06
WAZ	Shuttle run	988	-0.02 (-0.25, 0.22)	-0.01 (-0.24, 0.22)	-0.02 (-0.24, 0.2)	0.02 (-0.21, 0.24)	0	0.01
BMIZ	Shuttle run	988	-0.22 (-0.44, -0.01)	-0.22 (-0.44, -0.01)	-0.23 (-0.42, -0.04)	-0.18 (-0.37, 0)	-0.07	-0.06
Knee-heel length	Shuttle run	989	0.02 (-0.09, 0.13)	0.02 (-0.08, 0.13)	0.07 (-0.04, 0.19)	0.08 (-0.03, 0.2)	0.01	0.06
Head circumference	Shuttle run	990	0.04 (-0.08, 0.17)	0.04 (-0.08, 0.16)	-0.04 (-0.16, 0.08)	-0.03 (-0.15, 0.1)	0.02	-0.01
MUAC	Shuttle run	989	-0.23 (-0.37, -0.09)	-0.23 (-0.37, -0.09)	-0.18 (-0.31, -0.05)	-0.16 (-0.3, -0.03)	-0.11	-0.08
Waist circumference	Shuttle run	989	-0.03 (-0.08, 0.03)	-0.03 (-0.08, 0.03)	-0.03 (-0.09, 0.02)	-0.01 (-0.07, 0.04)	-0.03	-0.01
Hip circumference	Shuttle run	990	-0.07 (-0.11, -0.03)	-0.07 (-0.11, -0.03)	-0.04 (-0.09, 0)	-0.04 (-0.08, 0)	-0.1	-0.06
Calf circumference	Shuttle run	989	-0.12 (-0.24, -0.01)	-0.12 (-0.23, -0.01)	-0.08 (-0.19, 0.02)	-0.07 (-0.18, 0.04)	-0.08	-0.04
Lean mass index	Shuttle run	982	0.24 (0.1, 0.38)	0.24 (0.1, 0.38)	0.17 (0.03, 0.32)	0.22 (0.08, 0.36)	0.11	0.11
Impedance Index	Shuttle run	982	0.95 (0.26, 1.63)	0.96 (0.28, 1.64)	0.92 (0.17, 1.66)	1.14 (0.42, 1.86)	0.09	0.11
Phase angle	Shuttle run	982	0.07 (-0.25, 0.38)	0.06 (-0.25, 0.37)	0.22 (-0.06, 0.5)	0.27 (-0.01, 0.56)	0.01	0.06

Total Skinfold	Shuttle run	987	-0.08 (-0.1, -0.06)	-0.08 (-0.1, -0.06)	-0.07 (-0.1, -0.05)	-0.08 (-0.1, -0.06)	-0.18	-0.18
Peripheral Skinfold	Shuttle run	988	-0.11 (-0.15, -0.07)	-0.11 (-0.15, -0.07)	-0.11 (-0.15, -0.06)	-0.11 (-0.15, -0.07)	-0.15	-0.15
Central Skinfold	Shuttle run	989	-0.19 (-0.23, -0.14)	-0.19 (-0.23, -0.14)	-0.16 (-0.2, -0.12)	-0.17 (-0.21, -0.12)	-0.21	-0.19
Hb	Shuttle run	990	0.2 (0.08, 0.33)	0.2 (0.08, 0.33)	0.2 (0.07, 0.33)	0.21 (0.08, 0.34)	0.09	0.09

Table A4-10 Association of SAHARAN growth variables with shuttle run

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children’s books at home, caregiver education and gender norms

Growth Exposure x16	Outcome		GEE Mean difference (95% CI)					
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Systolic BP	988	1.33 (0.56, 2.11)	1.35 (0.59, 2.12)	1.32 (0.66, 1.99)	1.24 (0.55, 1.92)	0.13	0.11
WAZ	Systolic BP	986	1.95 (1.28, 2.62)	1.98 (1.31, 2.66)	1.77 (1.15, 2.4)	1.78 (1.16, 2.39)	0.18	0.17
BMIZ	Systolic BP	986	1.71 (0.99, 2.42)	1.72 (1.01, 2.43)	1.43 (0.77, 2.08)	1.52 (0.88, 2.15)	0.16	0.14
Knee-heel length	Systolic BP	987	0.78 (0.46, 1.11)	0.8 (0.48, 1.12)	0.61 (0.32, 0.9)	0.56 (0.26, 0.86)	0.17	0.12
Head circumference	Systolic BP	988	0.03 (-0.34, 0.4)	0.02 (-0.35, 0.39)	0.21 (-0.14, 0.55)	0.23 (-0.11, 0.57)	0.01	0.02
MUAC	Systolic BP	987	1.31 (0.89, 1.73)	1.31 (0.89, 1.73)	1.05 (0.65, 1.45)	1.21 (0.8, 1.62)	0.19	0.17
Waist circumference	Systolic BP	987	0.55 (0.36, 0.73)	0.55 (0.36, 0.73)	0.43 (0.27, 0.6)	0.42 (0.26, 0.58)	0.19	0.14
Hip circumference	Systolic BP	988	0.53 (0.38, 0.67)	0.53 (0.39, 0.68)	0.45 (0.31, 0.58)	0.38 (0.25, 0.52)	0.23	0.16
Calf circumference	Systolic BP	987	0.89 (0.55, 1.24)	0.9 (0.55, 1.24)	0.75 (0.42, 1.08)	0.77 (0.41, 1.12)	0.16	0.14
Lean mass index	Systolic BP	980	1.25 (0.81, 1.68)	1.23 (0.8, 1.67)	1.16 (0.76, 1.55)	1.29 (0.9, 1.68)	0.18	0.19
Impedance Index	Systolic BP	980	7.74 (5.59, 9.89)	7.75 (5.6, 9.91)	6.88 (4.74, 9.03)	7.06 (4.99, 9.14)	0.22	0.2
Phase angle	Systolic BP	980	2.08 (1.09, 3.06)	2.05 (1.07, 3.03)	1.1 (0.26, 1.95)	0.94 (0.09, 1.78)	0.13	0.06
Total Skinfold	Systolic BP	985	0.2 (0.1, 0.29)	0.2 (0.1, 0.3)	0.19 (0.1, 0.28)	0.15 (0.05, 0.25)	0.13	0.09

Peripheral Skinfold	Systolic BP	986	0.21 (0.05, 0.36)	0.22 (0.06, 0.38)	0.23 (0.09, 0.37)	0.16 (0, 0.31)	0.08	0.06
Central Skinfold	Systolic BP	987	0.57 (0.38, 0.75)	0.57 (0.38, 0.76)	0.46 (0.26, 0.65)	0.41 (0.2, 0.61)	0.19	0.13
Hb	Systolic BP	988	0 (-0.54, 0.53)	-0.01 (-0.55, 0.53)	-0.1 (-0.57, 0.38)	-0.01 (-0.49, 0.47)	0	0

Table A4-11 Association of SAHARAN growth variables with systolic blood pressure

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

Growth Exposure x16	Outcome		GEE Mean difference (95% CI)					
		n	Unadjusted	Model 1 (arm)	Model 2 (trial factors)	Model 3 (trial and contemporary covariates from DAG).	Standardised unadjusted coefficient	Standardised adjusted coefficient (chord diagram)
HAZ	Diastolic BP	988	1.13 (0.6, 1.67)	1.15 (0.62, 1.67)	1.07 (0.58, 1.55)	1.11 (0.6, 1.62)	0.14	0.13
WAZ	Diastolic BP	986	1.73 (1.18, 2.28)	1.77 (1.23, 2.32)	1.4 (0.89, 1.92)	1.55 (1.02, 2.08)	0.2	0.18
BMIZ	Diastolic BP	986	1.52 (0.93, 2.1)	1.54 (0.98, 2.1)	1.1 (0.58, 1.62)	1.25 (0.71, 1.8)	0.17	0.14
Knee-heel length	Diastolic BP	987	0.66 (0.44, 0.88)	0.67 (0.46, 0.89)	0.56 (0.33, 0.78)	0.57 (0.34, 0.8)	0.17	0.14
Head circumference	Diastolic BP	988	0.21 (-0.12, 0.54)	0.2 (-0.13, 0.53)	0.21 (-0.07, 0.49)	0.41 (0.1, 0.73)	0.04	0.08
MUAC	Diastolic BP	987	1.07 (0.75, 1.39)	1.07 (0.77, 1.38)	0.78 (0.46, 1.11)	0.96 (0.64, 1.28)	0.19	0.17
Waist circumference	Diastolic BP	987	0.42 (0.27, 0.56)	0.42 (0.28, 0.56)	0.3 (0.17, 0.43)	0.36 (0.21, 0.5)	0.17	0.15
Hip circumference	Diastolic BP	988	0.43 (0.3, 0.56)	0.44 (0.32, 0.57)	0.33 (0.22, 0.44)	0.34 (0.22, 0.46)	0.23	0.18
Calf circumference	Diastolic BP	987	0.7 (0.43, 0.96)	0.7 (0.44, 0.97)	0.49 (0.24, 0.75)	0.59 (0.31, 0.87)	0.16	0.13
Lean mass index	Diastolic BP	980	0.76 (0.43, 1.08)	0.74 (0.42, 1.06)	0.61 (0.22, 1)	0.81 (0.42, 1.19)	0.13	0.14
Impedance Index	Diastolic BP	980	5.31 (3.62, 6.99)	5.29 (3.63, 6.95)	4.48 (2.61, 6.34)	5.17 (3.35, 6.99)	0.18	0.18
Phase angle	Diastolic BP	980	1.86 (1.08, 2.63)	1.84 (1.07, 2.6)	0.99 (0.35, 1.63)	1.18 (0.54, 1.81)	0.14	0.09
Total Skinfold	Diastolic BP	985	0.13 (0.06, 0.19)	0.13 (0.07, 0.2)	0.14 (0.07, 0.21)	0.09 (0.03, 0.16)	0.11	0.08
Peripheral Skinfold	Diastolic BP	986	0.19 (0.07, 0.31)	0.2 (0.08, 0.32)	0.18 (0.06, 0.3)	0.17 (0.05, 0.29)	0.09	0.08

Central Skinfold	Diastolic BP	987	0.33 (0.22, 0.43)	0.33 (0.22, 0.43)	0.35 (0.23, 0.46)	0.18 (0.07, 0.29)	0.14	0.08
Hb	Diastolic BP	988	0.17 (-0.22, 0.56)	0.17 (-0.22, 0.56)	-0.05 (-0.4, 0.3)	0.19 (-0.19, 0.57)	0.03	0.03

Table A4-12 Association of SAHARAN growth variables with diastolic blood pressure

For the adjusted models, Model 1 adjusted for trial arm only. Model 2 adjusted for trial factors which were arm, sex, DC, calendar age recruited, age of child, ambient temperature. Model 3 adjusted for trial factors plus child schooling, discipline score, caregiver depression score (EPDS), Food insecurity (HFIAS), Religion, Socioeconomic status, social support, adversity, children's books at home, caregiver education and gender norms

A4-4 Principal components analysis

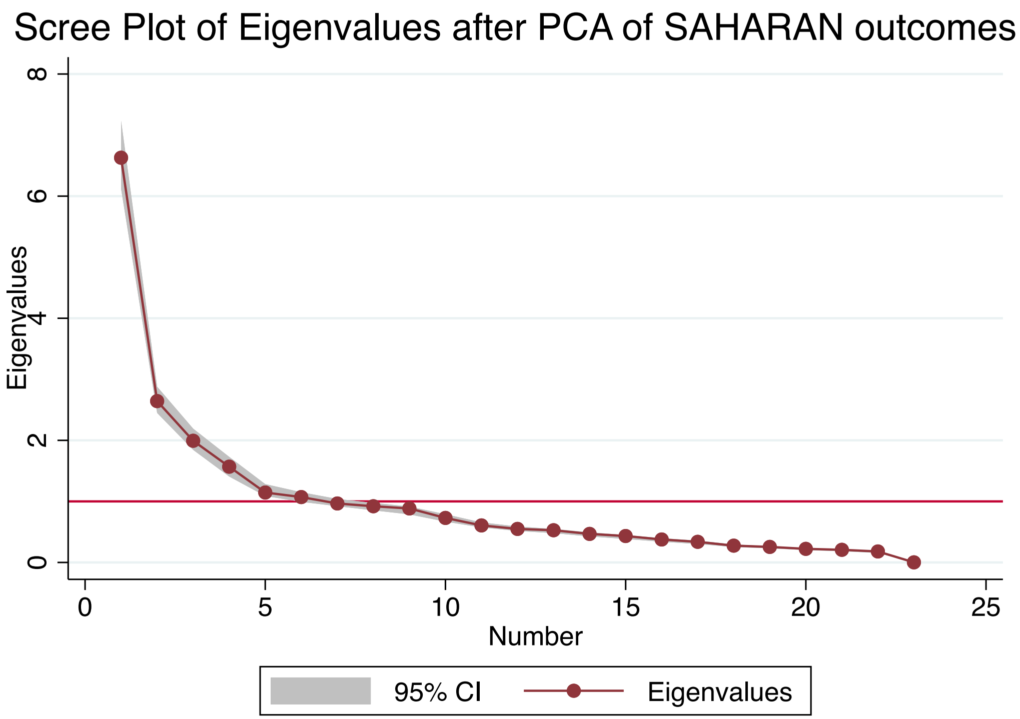


Figure A4-2 Scree plot

Scree plot showing number of Eigenvalues after principal components analysis of SAHARAN toolbox outcomes, suggesting 5 components.

A4-5 Hierarchical clustering analysis

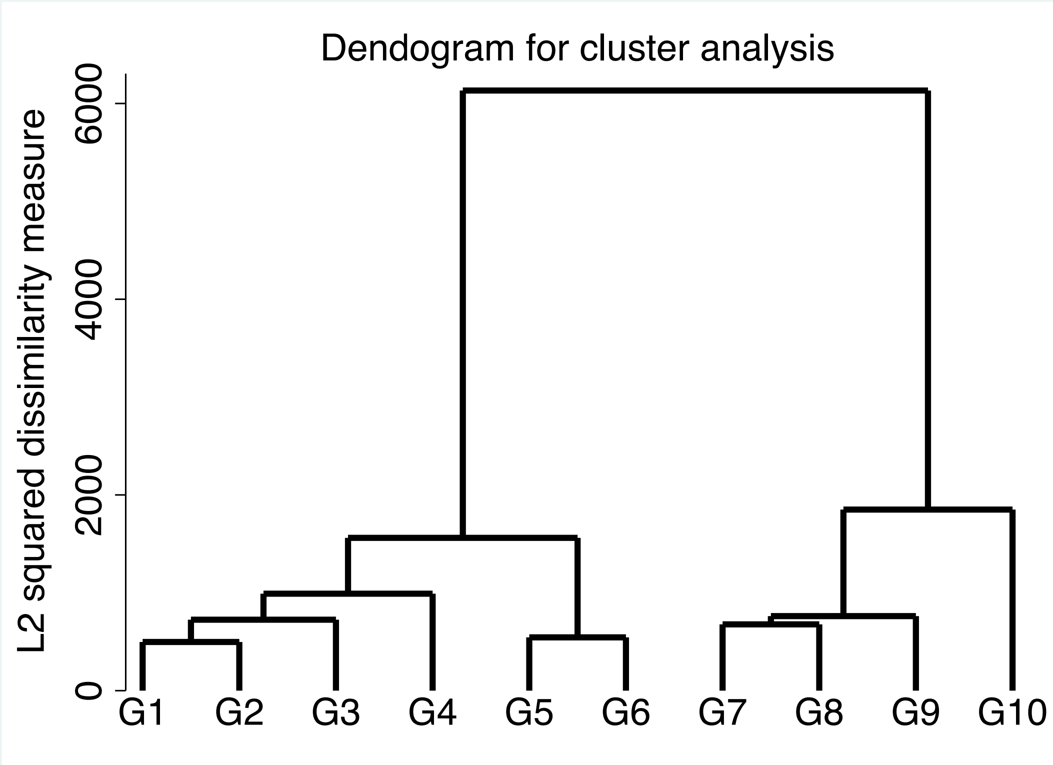


Figure A4-3 Dendogram from hierarchical cluster analysis of SAHARAN Toolbox outcomes,

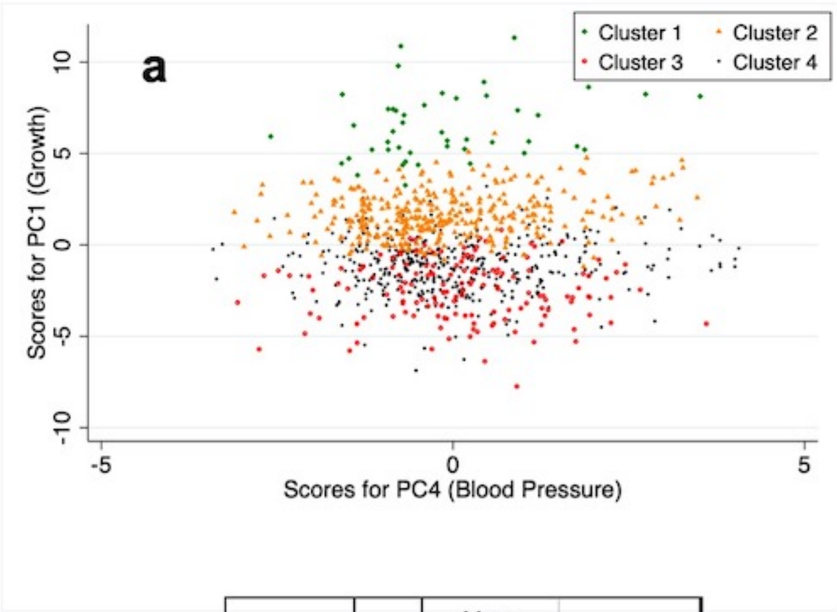
This dendogram suggested 4 clusters was appropriate.

Hierarchical Cluster number	% [number in each cluster]	% [female]	% [number in SoC arm]	% [number in IYCF arm]	% [number in WASH arm]	% [number in WASH & IYCF combined arm]
1	4.86% [46]	69.6% [32]	23.9% [11]	23.9% [11]	30.4% [14]	21.7% [10]
2	35.8% [339]	51.6% [175]	22.1% [75]	28.9% [98]	25.1% [85]	23.9% [81]
3	15.9% [151]	61.6% [93]	27.8% [42]	21.2% [32]	29.1% [44]	21.9% [33]
4	43.4% [411]	44.5% [183]	24.6% [101]	23.4% [96]	24.1% [99]	28.0% [115]
total	[947]	51% [483]	24.2% [229]	25.0% [237]	25.6% [242]	25.2% [239]

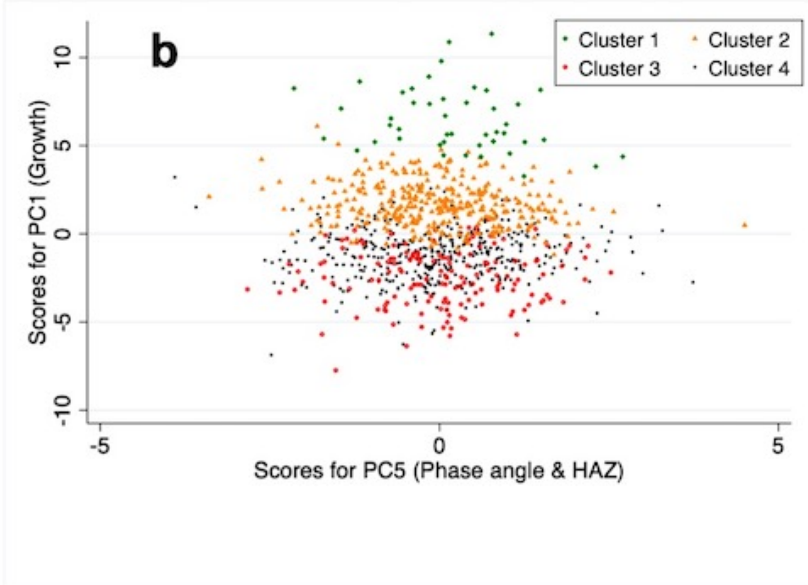
Table A4-13 Table describing distribution of children into hierarchical clusters.

The table shows proportion that were female and also distribution by intervention arm in the SHINE trial.

A4-6 Hierarchical cluster plots



Cluster	n	Mean Systolic BP (SD)	Mean Diastolic BP
1	46	100.7 (8.3)	64.8 (7.5)
2	339	98 (9.1)	63.2 (7.2)
3	151	93.9 (8.8)	60.2 (6.6)
4	411	96.6 (9.2)	61.9 (7.7)
Overall	947	96.9 (9.2)	62.3 (7.4)



Cluster	n	Mean HAZ (SD)	Mean BMI (SD)	Mean Phase angle (SD)
1	46	0.6 (0.8)	0.9 (0.6)	5.3 (0.5)
2	339	-0.1 (0.7)	-0.1 (0.6)	5 (0.6)
3	151	-1 (0.8)	-1.4 (0.7)	4.8 (0.5)
4	411	-0.8 (0.8)	-0.7 (0.6)	4.9 (0.5)
Overall	947	-0.5 (0.9)	62.3 (7.4)	4.9 (0.5)

Figure A4-4 Hierarchical clusters of PC1 (nutritional status) against a) PC4 and b) PC5.

PC4 represented blood pressure, PC5 represented HAZ and phase angle

A4-7 Distribution of contemporary, early-life and baseline variables by hierarchical cluster

Cluster	n	Mean HFIAS (SD)	Mean HDDS (SD)	Mean HWISE (SD)	Mean Adversity (SD)	Mean Child Schooling, yr (SD)	Mean Carer Schooling /yr (SD)	Mean Edinburgh postnatal depression score (SD)	Mean Social support (SD)	Mean Gender norms (SD)	Mean Discipline total (SD)	Mean Child parent relationship scale(SD)
1	46	11.2 (3.2)	7.8 (1.5)	12 (0.1)	1.7 (1.3)	3.6 (0.8)	10.8 (2.2)	2.4 (3.1)	4 (0.5)	4.2 (0.6)	2.1 (2)	3.5 (0.5)
2	339	12 (4.1)	7.7 (1.9)	12.2 (1.2)	1.7 (1.3)	3.4 (0.7)	10 (2.5)	3.2 (4.4)	3.9 (0.5)	4.2 (0.6)	1.9 (1.9)	3.4 (0.7)
3	151	12 (4.5)	7.8 (1.7)	12.1 (1)	1.8 (1.5)	3.4 (0.6)	**10.2 (2.7)**	**2.8 (4.1)**	3.8 (0.5)	4.1 (0.6)	1.9 (2)	3.4 (0.6)
4	411	12.1 (4.3)	7.6 (1.8)	12.1 (0.7)	1.8 (1.5)	3 (0.8)	9.9 (2.6)	3.4 (4.6)	3.9 (0.5)	4.1 (0.6)	1.9 (2)	3.3 (0.7)
Overall	947	12 (4.2)	7.7 (1.8)	12.1 (0.9)	1.8 (1.4)	3.3 (0.8)	10.0 (2.6)	3.2 (4.4)	3.9 (0.5)	4.1 (0.6)	1.9 (2)	3.3 (0.7)

Table A4-14 Distribution of contemporary covariates within the 4 hierarchical clusters.

Cluster	n	Mean birthweight (SD)	Mean LAZ at 18 mo (SD)	Mean WAZ at 18 mo (SD)	Mean WHZ at 18 mo (SD)	Mean HCZ at 18 mo (SD)	Mean MUACZ at 18mo (SD)	Mean Hb at 18 mo (SD)	Mean HCZ at 3 mo (SD)	Mean LAZ at 1 mo (SD)
1	46	3.3 (0.5)	-0.5 (1.1)	0.6 (1.1)	1.1 (1.2)	0.2 (1)	1 (0.9)	12.1 (1.1)	0.4 (0.9)	-0.4 (1.1)
2	339	3.2 (0.5)	-1.1 (0.9)	-0.3 (0.8)	0.3 (0.8)	0.1 (0.9)	0.4 (0.8)	11.8 (1.2)	0.1 (1.1)	-0.7 (1.3)
3	151	2.9 (0.4)	-2.0 (1.0)	-1.4 (0.9)	-0.6 (0.9)	-0.5 (1)	-0.4 (0.8)	11.7 (1.2)	-0.3 (1)	-1.3 (1.3)
4	411	3.1 (0.5)	-1.8 (0.9)	-1 (0.8)	-0.2 (0.9)	-0.4 (0.9)	-0.1 (0.8)	11.7 (1.1)	-0.2 (1.2)	-1.1 (1.2)
Overall	903	3.1 (0.5)	-1.5 (1)	-0.7 (1)	0 (1)	-0.2 (1)	0.1 (0.9)	11.8 (1.1)	-0.1 (1.1)	-1.0 (1.3)

Table A4-15 Distribution of early-life growth measures within the 4 hierarchical clusters

Cluster	n	Household size (SD)	Socioeconomic status (SD)	Mean CSI (SD)	Maternal age (SD)	Mean maternal height (SD)	Mean maternal MUAC (SD)	Mean maternal Hb (SD)	Mean maternal years schooling (SD)	Mean parity (SD)	Mean baseline gender norms (SD)	Mean baseline social support (SD)
1	46	5.2 (2.3)	0.1 (1.9)	5.1 (11.2)	25.5 (7.1)	161.9 (6.5)	28 (3.7)	12.1 (1.3)	10 (1.4)	1.9 (1.5)	2.0 (0.7)	3.5 (0.5)
2	321	5.1 (2.0)	0.3 (1.7)	3.7 (8.7)	26.2 (6.3)	161.1 (5.8)	27.3 (3.4)	12.2 (1.4)	9.7 (1.7)	1.7 (1.3)	2.3 (0.8)	3.6 (0.6)
3	147	5.5 (2.4)	0.5 (1.9)	3.8 (7.8)	26 (6.7)	159.2 (5.4)	25.6 (3.0)	12.1 (1.5)	10.1 (1.4)	1.9 (1.7)	2.4 (0.8)	3.6 (0.7)
4	398	5.1 (2.5)	0.0 (1.8)	5.3 (9.1)	25.4 (6.1)	159 (6.1)	26.1 (3.0)	12.1 (1.4)	9.5 (1.8)	1.7 (1.4)	2.4 (0.8)	3.5 (0.6)
Overall	912	5.1 (2.3)	0.2 (1.8)	4.4 (8.9)	25.8 (6.3)	159.9 (6.0)	26.6 (3.3)	12.2 (1.4)	9.7 (1.7)	1.8 (1.4)	2.3 (0.8)	3.5 (0.6)

Table A4-16 Distribution of baseline covariates within the 4 hierarchical clusters

Note that baseline covariates were measured during the pregnancy of the child born into the SHINE stud

9.3 A5: Chapter 5 appendix

A5-1 Baseline characteristics of SFU compared to the rest of SHINE

Household characteristics for children born to HIV negative mothers (CHU)	CHU included in SFU (1002)	CHU Not included in SFU (2987)	p-value
Number of Caregivers	988	2949	
Number of Children, N	1002	2987	
Women completing baseline visit, N	922	2767	
Household size			
Median number of occupants [IQR]	5.0 (4.0; 6.0)	5.5 (3.0 ; 6.0)	0.09
Wealth quintile, percent [n]			
Lowest	164/914 (17.9%)	511/2744 (18.6%)	0.84
Second	168/914 (18.4%)	544/2744 (19.8%)	
Middle	186/914 (20.4%)	553/2744 (20.2%)	
Fourth	200/914 (21.9%)	576/2744 (21.0%)	
Highest	196/914 (21.4%)	560/2744 (20.4%)	
Electricity			
Electricity, yes n (%)	31/914 (3.4%)	69/2738 (2.5%)	0.18
Other electric power			
Generator	32/914 (3.5%)	86/2743 (3.1%)	0.21
Solar panel	631/914 (69.0%)	1795/2743 (65.4%)	
Inverter	13/914 (1.4%)	44/ 2743 (1.6%)	
No other type	238/914 (26.0%)	818/2743 (29.8%)	
Sanitation			
Any latrine at household	343/899 (38.2%)	981/2707 (36.2%)	0.42
Improved latrine at household	290/898 (32.3%)	867/2703 (32.1%)	0.92
Water			
Main source of household drinking water improved	618/900 (68.7%)	1675/2725 (61.5%)	0.01
Treat drinking water to make it safer	127/895 (14.2%)	322/2673 (12.1%)	0.12
One-way walk time to fetch drinking water (min) , median (IQR)	10.0 (5.0 ; 20.0)	10.0 (5.0 ; 20.0)	0.30
Per capita water volume collected past 24 hr, median (IQR)	6.7 (4.4 ; 10.0)	7.5 (5.0 ; 12.0)	<0.001
Hygiene			
Handwashing station at household	101/876 (11.5%)	207/2557 (8.1%)	0.01
Improved floor	484/900 (53.8%)	1512/2707 (55.9%)	0.44
Number of chickens, median (IQR)	6.0 (2.0 ; 10.0)	6.0 (2.0 ; 10.0)	0.12
Livestock observed inside the house	390/963 (40.5%)	1039/2886 (36.0%)	0.02
Faeces observed in the yard	322/958 (33.6%)	877/2879 (30.5%)	0.15
Diet quality and food security			
Household meets minimum dietary diversity score	328/880 (37.3%	965/2344 (41.2%)	0.095
Coping strategies index, median (IQR)	0.0 (0.0 ; 6.0)	1.0 (0.0 ; 7.0)	0.01

Table A5-1 Baseline household characteristics for SFU and the rest of the SHINE cohort.

This was for children born to mothers without HIV who were enrolled to SHINE follow-up, compared to those who were not enrolled. IQR (inter-quartile range)

Maternal characteristics for children born to HIV negative mothers (CHU)	CHU included in SFU (1002)	CHU Not included in SFU (2987)	p-value
Maternal anthropometry & demographics			
Mean maternal age (SD), years	25.7 (6.3)	25.6 (6.7)	0.15
Mean maternal height (SD), cm]	159.9 (6.0)	160.2 (5.6)	0.08
Mean maternal MUAC SD), cm	26.6 (3.3)	26.3 (3.0)	0.05
Mean Maternal Haemoglobin (SD)	12.2 (1.4)	12.1 (1.5)	0.21
Mother meets minimum dietary diversity score	330/901 (36.6%)	1081/2675 (40.4%)	0.10
Mean years of schooling completed (SD)	9.7 (1.7)	9.6 (1.8)	0.10
Median parity (IQR)	2.0 (1.0 ; 3.0)	2.0 (1.0 ; 3.0)	0.03
Married	889/935 (95.1%)	2657/2782 (95.5%)	0.29
Employed	69/916 (7.5%)	242/2739 (8.8%)	0.23
Maternal Religion			
Apostolic	455/941 (48.4%)	1308/2804 (46.7%)	0.10
Other Christian	395/941 (42.0%)	1289/2804 (46.0%)	
Other religion	91/941 (9.7%)	207/2804 (7.4%)	
Maternal Capabilities			
Median Gender norms and attitudes (IQR)	2.3 (1.5 ; 3.0)	1.7 (1.5 ; 3.0)	<0.001
Median Perceived social support (IQR)	3.6 (3.2 ; 4.0)	3.7 (3.3 ; 4.0)	0.05
Median EPDS depression scale (IQR)	1.0 (0.0 ; 5.0)	1.0 (0.0 ; 4.0)	0.81

Table A5-2 Baseline maternal characteristics for SFU and the rest of the SHINE cohort.

Maternal characteristics for children born to HIV negative mothers who were enrolled to SHINE follow-up, compared to those who were not enrolled. IQR (inter-quartile range), MUAC: Mid upper arm circumference

Child characteristics for children born to HIV negative mothers (CHU)	CHU included in SFU (1002)	CHU Not included in SFU (2987)	p-value
Female, percent	**511/1002 (51.0%)**	**1451/2972 (48.8%)**	**0.28**
Child characteristics at birth			
Mean birth weight (SD), kg	**3.1 (0.5)**	**3.1 (0.5)**	**0.43**
Low birthweight	**90/957 (9.4%)**	**235/2616 (9.0%)**	**0.74**
Institutional delivery	**855/935 (91.4%)**	**2353/2669 (88.2%)**	**0.01**
Vaginal delivery	**909/965 (94.2%)**	**2482/2699 (92.0%)**	**0.10**
Child characteristics at 18 months of age			
Mean LAZ at 18 months, (SD)	**-1.5 (1.0)**	**-1.5 (1.1)**	**0.18**
Mean WAZ at 18 months, (SD)	**-0.7 (1.0)**	**-0.7 (1.0)**	**0.06**
Mean WHZ at 18 months, (SD)	**-0.0 (1.0)**	**0.1 (1.1)**	**0.001**
Mean Head Circ at 18 months, (SD)	**-0.2 (1.1)**	**-0.2 (1.5)**	**0.48**
Mean MUAC at 18 months, (SD)	**0.1 (0.9)**	**0.0 (0.9)**	**0.03**
Mean Hb at 18 months, (SD)	**11.8 (1.1)**	**11.7 (1.2)**	**0.11**

Table A5-3 Baseline child characteristics for SFU and the rest of the SHINE cohort.

Child characteristics for children born to HIV negative mothers who were enrolled to SHINE follow-up, compared to those who were not enrolled. IQR (inter-quartile range), head circ (head circumference, MUAC: Mid-upper arm circumference, Hb: haemoglobin

A5-2 Early-life growth on 7-year Outcomes: Directed Acyclic Graph

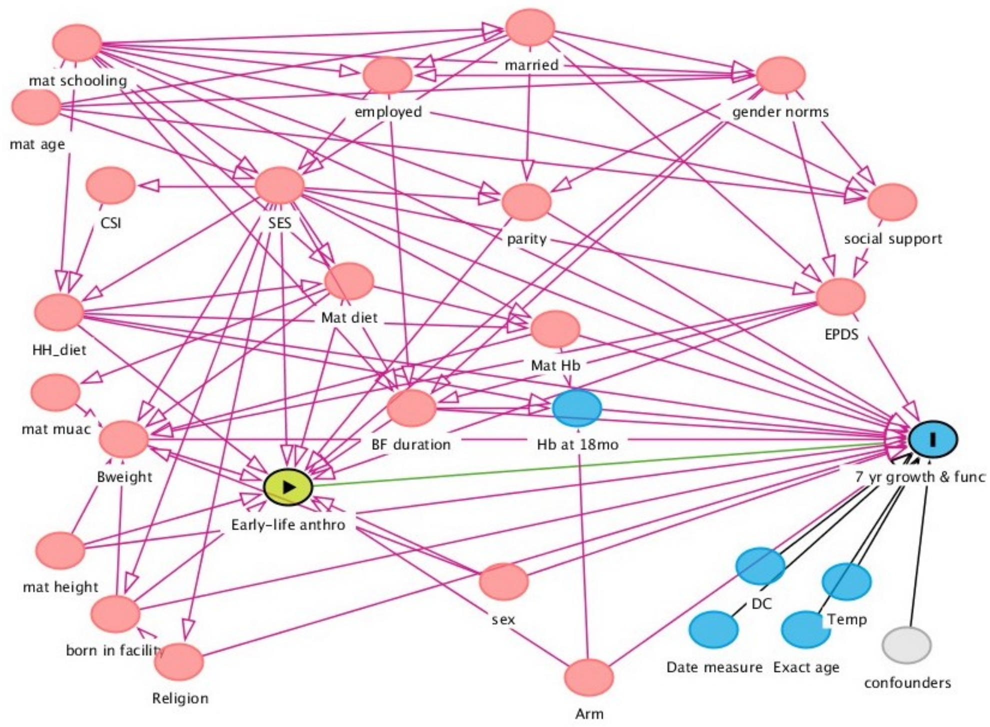


Figure A5-1 DAG describing effect of early-life anthropometry on SAHARAN outcomes

Directed acyclic graph (DAG) for early-life anthropometry's effect on 7 year growth and function with early-life covariates. This DAG was used to identify the confounding variables that were required within the adjusted model for examining early-life anthropometry on school-age outcomes. Hence the model exploring the effect of early-life anthropometry on 7 year growth and function included the following co-variates arm, sex, data collector, ambient temperature, date measured, breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height, maternal schooling.

A5-3 Early-life Length on 7-year SAHARAN Toolbox outcomes

Associations of LAZ at 1 month with SAHARAN Toolbox Outcomes

Early-life exposure: Length-for-Age Z-score at 1 month	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	Adjusted (Chord)
LAZ at 1 month	MPI	545	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	**534**	**0 (-1, 1)**	**0.01**	**0.00**
LAZ at 1 month	SAT	549	1 (-1, 2)	1 (-1, 2)	1 (-1, 2)	**534**	**0 (-1, 2)**	**0.01**	**0.01**
LAZ at 1 month	Plus EF	537	1 (-1, 2)	1 (-1, 2)	1 (-1, 2)	**526**	**1 (-1, 2)**	**0.02**	**0.03**
LAZ at 1 month	Fine motor	543	-0.2 (-0.7, 0.3)	-0.2 (-0.7, 0.3)	-0.2 (-0.7, 0.3)	**534**	**-0.1 (-0.5, 0.4)**	**-0.02**	**-0.01**
LAZ at 1 month	SDQ	549	0 (0, 1)	0 (0, 1)	0 (0, 1)	**534**	**0 (0, 1)**	**0.09**	**0.11**
LAZ at 1 month	Child Socioem	546	0 (0, 0)	0 (0, 0)	0 (0, 0)	523	**0 (0, 0)**	0.03	**0.04**
LAZ at 1 month	**Grip strength**	**546**	**0.2 (0.0, 0.3)**	**0.2 (0.0, 0.3)**	**0.2 (0.1, 0.3)**	**534**	**0.2 (0.1, 0.3)**	**0.09**	**0.10**
LAZ at 1 month	Broad jump	545	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.2 (0.3, 2.1)	**534**	**1 (0.1, 1.8)**	**0.06**	**0.07**
LAZ at 1 month	Shuttle run	549	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.3)	**532**	**0.1 (0.0, 0.3)**	**0.03**	**0.06**
LAZ at 1 month	Diastolic BP	549	0.1 (-0.4, 0.5)	0.1 (-0.3, 0.5)	0 (-0.4, 0.4)	**534**	**0.1 (-0.3, 0.6)**	**0.02**	**0.02**
LAZ at 1 month	Systolic BP	548	0.4 (-0.2, 1.1)	0.4 (-0.2, 1.0)	0.4 (-0.2, 1.0)	**534**	**0.4 (-0.2, 1.0)**	**0.07**	**0.07**
LAZ at 1 month	**HAZ**	**548**	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	**534**	**0.2 (0.2, 0.3)**	**0.34**	**0.33**
LAZ at 1 month	**WAZ**	**548**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.2)**	**534**	**0.2 (0.1, 0.2)**	**0.28**	**0.26**
LAZ at 1 month	BMI	549	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	**534**	**0.0 (0.0, 0.1)**	**0.08**	**0.05**
LAZ at 1 month	**Knee-heel**	**549**	**0.5 (0.3, 0.6)**	**0.5 (0.3, 0.6)**	**0.5 (0.3, 0.6)**	**534**	**0.4 (0.3, 0.6)**	**0.28**	**0.27**
LAZ at 1 month	**Head circ**	**549**	**0.2 (0, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**534**	**0.2 (0.1, 0.3)**	**0.12**	**0.16**
LAZ at 1 month	**MUAC**	**548**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	**0.1 (0, 0.2)**	**534**	**0.1 (0, 0.2)**	**0.12**	**0.08**
LAZ at 1 month	**Waist circ**	**548**	**0.3 (0.1, 0.4)**	**0.2 (0.1, 0.4)**	**0.3 (0.1, 0.5)**	**533**	**0.3 (0.1, 0.5)**	**0.10**	**0.10**
LAZ at 1 month	**Hip circ**	**549**	**0.5 (0.3, 0.8)**	**0.5 (0.3, 0.8)**	**0.5 (0.3, 0.7)**	**534**	**0.5 (0.2, 0.7)**	**0.16**	**0.14**
LAZ at 1 month	**Calf circ**	**545**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**534**	**0.2 (0.1, 0.3)**	**0.18**	**0.15**
LAZ at 1 month	LMI	544	0.0 (-0.1, 0.1)	0 .0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	**530**	**0.0 (0.0, 0.1)**	**0.00**	**0.01**
LAZ at 1 month	**Imp Index**	**545**	**0.0 (0.0, 0.1)**	**0.0 (0.0, 0.1)**	**0.0 (0.0, 0.1)**	**530**	**0.0 (0.0, 0.1)**	**0.18**	**0.19**
LAZ at 1 month	Phase angle	547	0.0 (-0.1, 0.0)	0.0 (-0.1, 0.0)	0.0 (-0.1, 0.0)	**530**	**0.0 (-0.1, 0.0)**	**-0.08**	**-0.09**
LAZ at 1 month	Total SFT	548	0.4 (0.0, 0.8)	0.4 (0.0, 0.8)	0.2 (-0.2, 0.5)	**533**	**0.2 (-0.2, 0.5)**	**0.07**	**0.03**
LAZ at 1 month	**Periphl SFT**	**548**	**0.3 (0.1, 0.6)**	**0.3 (0.1, 0.6)**	**0.2 (0.0, 0.4)**	**533**	**0.2 (0.0, 0.4)**	**0.11**	**0.07**
LAZ at 1 month	Central SFT	549	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.2)	0 (-0.2, 0.1)	**534**	**-0.1 (-0.3, 0.1)**	**0.02**	**-0.03**
LAZ at 1 month	Hb	545	-0.1 (-0.2, 0.0)	-0.1 (-0.2, 0.0)	-0.1 (-0.2, 0.0)	**534**	**-0.1 (-0.2, 0.0)**	**-0.09**	**-0.12**

Table A5-4 Associations of length-for-age Z-score (LAZ) at 1 month with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 Ohms^{-1}, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

Associations of stunted children at 1 month with SAHARAN Toolbox Outcomes

Early-life Exposure	Outcome	Not stunted		Stunted		GEE Mean difference (95% CI)				
Stunted at 1 months (LAZ < -2) at 1 moth		N1	Mean (SD)	N2	Mean (SD)	Unadjusted	Model 1 (arm)	Model 2 (a)	N for model3	Model 3
Stunted at 1 mo	MPI	439	48 (11)	103	48 (11)	-1 (-3, 2)	-1 (-3, 2)	-1 (-3, 2)	534	0 (-3, 2)
Stunted at 1 mo	SAT	439	45 (27)	103	43 (28)	-3 (-9, 3)	-3 (-9, 3)	-3 (-9, 3)	534	-3 (-9, 2)
Stunted at 1 mo	Plus EF	431	114 (24)	103	113 (25)	-2 (-6, 3)	-2 (-6, 3)	-3 (-7, 2)	526	-3 (-7, 2)
Stunted at 1 mo	Fine motor	439	24.2 (6.7)	103	23.8 (6.4)	-0.3 (-1.6, 1)	-0.3 (-1.6, 1)	-0.1 (-1.4, 1.2)	534	-0.2 (-1.4, 1)
Stunted at 1 mo	SDQ	439	9 (5)	103	8 (5)	0 (-2, 1)	0 (-2, 1)	-1 (-2, 1)	534	-1 (-2, 1)
Stunted at 1 mo	Child socioem	431	4 (1)	100	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	523	0 (0, 0)
Stunted at 1 mo	Grip strength	439	10.7 (1.9)	103	10.4 (2)	-0.3 (-0.7, 0.1)	-0.3 (-0.7, 0.2)	-0.4 (-0.8, 0)	534	-0.4 (-0.8, 0)
Stunted at 1 mo	Broad jump	439	112.1 (15.1)	103	109.2 (15.5)	-2.9 (-6.2, 0.3)	-2.9 (-6.2, 0.4)	-2.9 (-5.8, 0)	534	-2.8 (-5.7, 0)
Stunted at 1 mo	Shuttle run	437	51 (2.7)	103	50.9 (2.4)	-0.1 (-0.7, 0.5)	-0.1 (-0.7, 0.5)	-0.2 (-0.8, 0.4)	532	-0.3 (-0.9, 0.3)
Stunted at 1 mo	Diastolic BP	439	62.3 (7.5)	103	61.8 (7.5)	-0.4 (-1.9, 1)	-0.4 (-1.9, 1)	-0.1 (-1.5, 1.3)	534	-0.1 (-1.6, 1.3)
Stunted at 1 mo	Systolic BP	439	97.1 (9.4)	103	95.6 (9.9)	-1.5 (-3.5, 0.6)	-1.5 (-3.5, 0.6)	-0.7 (-2.6, 1.3)	534	-0.7 (-2.7, 1.3)
Stunted at 1 mo	**HAZ**	**439**	**-0.4 (0.8)**	**103**	**-1 (0.8)**	**-0.5 (-0.7, -0.4)**	**-0.5 (-0.7, -0.4)**	**-0.5 (-0.7, -0.4)**	**534**	**-0.5 (-0.7, -0.4)**
Stunted at 1 mo	**WAZ**	**439**	**-0.5 (0.8)**	**103**	**-1 (0.8)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.6, -0.3)**	**534**	**-0.4 (-0.6, -0.3)**
Stunted at 1 mo	**BMI**	**439**	**-0.5 (0.8)**	**103**	**-0.6 (0.7)**	**-0.2 (-0.4, 0)**	**-0.2 (-0.4, 0)**	**-0.1 (-0.3, 0)**	**534**	**-0.1 (-0.3, 0)**
Stunted at 1 mo	**Knee-heel**	**439**	**37.5 (1.7)**	**103**	**36.6 (1.7)**	**-0.9 (-1.3, -0.6)**	**-1 (-1.3, -0.6)**	**-1 (-1.3, -0.7)**	**534**	**-0.9 (-1.2, -0.6)**
Stunted at 1 mo	**Head circ**	**439**	**51.4 (1.4)**	**103**	**51 (1.4)**	**-0.4 (-0.7, -0.1)**	**-0.4 (-0.7, -0.1)**	**-0.5 (-0.8, -0.3)**	**534**	**-0.5 (-0.8, -0.3)**
Stunted at 1 mo	**MUAC**	**439**	**16.9 (1.3)**	**103**	**16.5 (1.1)**	**-0.4 (-0.7, -0.2)**	**-0.4 (-0.7, -0.2)**	**-0.3 (-0.6, -0.1)**	**534**	**-0.3 (-0.5, -0.1)**
Stunted at 1 mo	**Waist circ**	**438**	**54.2 (2.9)**	**103**	**53.2 (2.7)**	**-0.9 (-1.5, -0.4)**	**-0.9 (-1.5, -0.4)**	**-0.9 (-1.5, -0.4)**	**533**	**-0.9 (-1.5, -0.4)**
Stunted at 1 mo	**Hip circ**	**439**	**61.2 (3.9)**	**103**	**59.6 (3)**	**-1.6 (-2.3, -0.9)**	**-1.5 (-2.2, -0.9)**	**-1.4 (-2, -0.7)**	**534**	**-1.4 (-2.1, -0.8)**
Stunted at 1 mo	**Calf circ**	**439**	**23.5 (1.6)**	**103**	**22.9 (1.6)**	**-0.6 (-0.9, -0.2)**	**-0.6 (-0.9, -0.2)**	**-0.5 (-0.8, -0.2)**	**534**	**-0.5 (-0.8, -0.2)**
Stunted at 1 mo	LMI	435	12.1 (1.3)	103	12 (1.2)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	530	-0.1 (-0.3, 0.2)
Stunted at 1 mo	**Imp Index**	**435**	**1.8 (0.2)**	**103**	**1.7 (0.2)**	**-0.1 (-0.1, -0.1)**	**-0.1 (-0.1, -0.1)**	**-0.1 (-0.1, -0.1)**	**530**	**-0.1 (-0.1, 0)**
Stunted at 1 mo	Phase angle	435	5 (0.6)	103	5 (0.6)	0 (-0.2, 0.1)	0 (-0.2, 0.1)	0 (-0.2, 0.1)	530	0 (-0.2, 0.1)
Stunted at 1 mo	Total SFT	437	27.2 (6.2)	103	26.5 (5.7)	-0.7 (-2.1, 0.6)	-0.7 (-2, 0.7)	-0.2 (-1.5, 1.1)	533	-0.2 (-1.4, 1)
Stunted at 1 mo	Peripheral SFT	438	16.4 (3.7)	103	15.7 (3.4)	-0.7 (-1.5, 0.2)	-0.6 (-1.5, 0.2)	-0.4 (-1.1, 0.4)	533	-0.4 (-1.1, 0.4)
Stunted at 1 mo	Central SFT	438	10.9 (3)	103	10.7 (2.7)	-0.1 (-0.8, 0.5)	-0.1 (-0.7, 0.5)	0.1 (-0.5, 0.8)	534	0.2 (-0.4, 0.8)
Stunted at 1 mo	Hb	439	12.6 (1.2)	103	12.8 (1.2)	0.2 (-0.1, 0.4)	0.2 (-0.1, 0.4)	0.2 (-0.1, 0.4)	534	0.2 (-0.1, 0.4)

Table A5-5 Associations of Stunted children at 1 month (LAZ <-2) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

	Not stunted at 18 months (LAZ > -2)	Stunted at 18 months (LAZ< -2)	Total	P-value
Not stunted at 1 month	346 (89.9%)	89 (58.6%)	435	
Stunted at 1 month	39 (10.1%)	63 (41.4%)	102	
Total	385	152	537	<0.001

Table A5-6 Proportions of stunted and underweight children at 1 month and 18 months in the SHINE follow-up cohort.

Note the numbers are reduced due to missing data

Associations of LAZ at 18 months with SAHARAN Toolbox Outcomes

Early-life exposure: Length-for-Age Z-score at 18 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
LAZ at 18 months	MPI	981	**1 (0, 2)**	**1 (0, 2)**	**1 (0, 2)**	971	**1 (0, 2)**	**0.08**	**0.08**
LAZ at 18 months	SAT	981	**3 (1, 5)**	**3 (1, 5)**	**3 (1, 4)**	971	**3 (1, 4)**	**0.11**	**0.10**
LAZ at 18 months	Plus EF	969	1 (0, 3)	1 (0, 3)	1 (0, 3)	959	1 (0, 3)	0.06	0.06
LAZ at 18 months	Fine motor	977	-0.3 (-0.8, 0.2)	-0.4 (-0.8, 0.1)	-0.2 (-0.7, 0.2)	967	-0.2 (-0.7, 0.2)	-0.05	-0.03
LAZ at 18 months	SDQ	980	0 (0, 0)	0 (0, 0)	0 (0, 0)	970	0 (0, 0)	-0.02	-0.01
LAZ at 18 months	Child Socioem	964	0 (0, 0)	0 (0, 0)	0 (0, 0)	954	0 (0, 0)	0.03	0.03
LAZ at 18 months	**Grip strength**	**981**	**0.7 (0.5, 0.8)**	**0.6 (0.5, 0.8)**	**0.7 (0.6, 0.8)**	971	**0.7 (0.6, 0.8)**	**0.35**	**0.38**
LAZ at 18 months	**Broad jump**	**978**	**2.5 (1.7, 3.3)**	**2.5 (1.7, 3.4)**	**2.7 (1.9, 3.5)**	968	**2.7 (1.9, 3.5)**	**0.17**	**0.18**
LAZ at 18 months	**Shuttle run**	**978**	**0.3 (0.1, 0.5)**	**0.3 (0.1, 0.5)**	**0.2 (0.0, 0.4)**	967	**0.2 (0.0, 0.4)**	**0.10**	**0.09**
LAZ at 18 months	**Diastolic BP**	**979**	**0.6 (0.2, 1.0)**	**0.6 (0.2, 1.0)**	**0.6 (0.3, 1.0)**	969	**0.6 (0.2, 1.0)**	**0.08**	**0.09**
LAZ at 18 months	**Systolic BP**	**979**	**0.8 (0.1, 1.4)**	**0.8 (0.2, 1.4)**	**1.0 (0.4, 1.6)**	969	**1.0 (0.4, 1.6)**	**0.09**	**0.12**
LAZ at 18 months	**HAZ**	**981**	**0.6 (0.6, 0.7)**	**0.6 (0.6, 0.7)**	**0.6 (0.6, 0.7)**	971	**0.6 (0.6, 0.7)**	**0.74**	**0.74**
LAZ at 18 months	**WAZ**	**979**	**0.5 (0.5, 0.6)**	**0.5 (0.5, 0.6)**	**0.5 (0.5, 0.6)**	969	**0.5 (0.5, 0.5)**	**0.62**	**0.61**
LAZ at 18 months	**BMI**	**979**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	969	**0.1 (0.1, 0.2)**	**0.18**	**0.18**
LAZ at 18 months	**Knee-heel**	**980**	**1.2 (1.1, 1.3)**	**1.2 (1.1, 1.3)**	**1.3 (1.2, 1.3)**	970	**1.3 (1.2, 1.3)**	**0.66**	**0.67**
LAZ at 18 months	**Head circ**	**981**	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.4)**	**0.3 (0.3, 0.4)**	971	**0.3 (0.3, 0.4)**	**0.2**	**0.24**
LAZ at 18 months	**MUAC**	**980**	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	970	**0.4 (0.3, 0.5)**	**0.34**	**0.32**
LAZ at 18 months	**Waist circ**	**980**	**1.0 (0.8, 1.2)**	**1.0 (0.8, 1.2)**	**1.1 (0.9, 1.3)**	970	**1.1 (0.9, 1.2)**	**0.34**	**0.35**
LAZ at 18 months	**Hip circ**	**981**	**1.7 (1.4, 1.9)**	**1.7 (1.4, 1.9)**	**1.7 (1.5, 1.9)**	971	**1.7 (1.4, 1.9)**	**0.44**	**0.44**
LAZ at 18 months	**Calf circ**	**980**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	970	**0.6 (0.5, 0.7)**	**0.41**	**0.40**
LAZ at 18 months	**LMI**	**973**	**0.2 (0.1, 0.2)**	**0.2 (0.1, 0.2)**	**0.2 (0.1, 0.2)**	963	**0.2 (0.1, 0.2)**	**0.13**	**0.14**
LAZ at 18 months	**Imp Index**	**973**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	963	**0.1 (0.1, 0.1)**	**0.50**	**0.52**
LAZ at 18 months	Phase angle	973	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	963	0.0 (0.0, 0.1)	0.04	0.04
LAZ at 18 months	**Total SFT**	**978**	**1.2 (0.8, 1.6)**	**1.2 (0.8, 1.6)**	**1.1 (0.7, 1.5)**	969	**1.1 (0.6, 1.5)**	**0.21**	**0.18**
LAZ at 18 months	**Periphl SFT**	**979**	**0.8 (0.5, 1.0)**	**0.8 (0.5, 1.0)**	**0.6 (0.4, 0.9)**	969	**0.6 (0.4, 0.9)**	**0.21**	**0.18**
LAZ at 18 months	**Central SFT**	**980**	**0.5 (0.3, 0.8)**	**0.5 (0.3, 0.8)**	**0.5 (0.2, 0.7)**	971	**0.4 (0.2, 0.7)**	**0.18**	**0.15**
LAZ at 18 months	Hb	981	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	971	0.0 (-0.1, 0.1)	0.01	0.02

Table A5-7 Associations of length-for-age Z-score (LAZ at 18 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

Note that the value of 0.74 between LAZ at 18 months and HAZ at 7 years was the largest association measured for early life measures.

Associations of Stunted children at 18 months with SAHARAN Toolbox Outcomes

Early-life Exposure	Outcome	Not stunted at 18 months		Stunted at 18 months		GEE Mean difference (95% CI)				
Stunted at 18 months (LAZ < -2)		N1	Mean (SD)	N2	Mean (SD)	Unadjusted	Model 1 (arm)	Model 2	N for model3	Model 3
stunted at 18 mo	MPI	691	49 (11)	290	47 (11)	**-2 (-4, 0)**	**-2 (-4, 0)**	**-2 (-3, 0)**	971	**-2 (-3, 0)**
stunted at 18 mo	SAT	691	48 (28)	290	42 (27)	**-6 (-10, -1)**	**-6 (-10, -1)**	**-5 (-9, -1)**	971	**-5 (-8, -1)**
stunted at 18 mo	Plus EF	682	115 (23)	287	113 (26)	-2 (-6, 1)	-2 (-6, 1)	-3 (-6, 0)	959	-3 (-6, 0)
stunted at 18 mo	Fine motor	690	23.8 (6.4)	287	24.6 (7)	0.8 (-0.3, 1.9)	0.9 (-0.2, 2)	0.6 (-0.3, 1.6)	967	0.6 (-0.3, 1.6)
stunted at 18 mo	SDQ	690	9 (5)	290	9 (5)	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	970	0 (-1, 1)
stunted at 18 mo	Child socioem	679	4 (1)	285	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	954	0 (0, 0)
stunted at 18 mo	**Grip strength**	**691**	**11 (1.9)**	**290**	**10 (1.8)**	**-1 (-1.3, -0.8)**	**-1 (-1.3, -0.7)**	**-1.1 (-1.4, -0.9)**	971	**-1.1 (-1.4, -0.8)**
stunted at 18 mo	**Broad jump**	**690**	**114.2 (15.2)**	**288**	**109.5 (14.4)**	**-4.7 (-6.8, -2.6)**	**-4.8 (-6.9, -2.7)**	**-4.8 (-6.8, -2.8)**	968	**-4.8 (-6.8, -2.9)**
stunted at 18 mo	**Shuttle run**	**689**	**51 (2.8)**	**289**	**50.5 (2.5)**	**-0.5 (-0.9, -0.1)**	**-0.5 (-0.9, -0.2)**	**-0.5 (-0.9, -0.1)**	967	**-0.5 (-0.9, -0.1)**
stunted at 18 mo	Diastolic BP	690	62.5 (7.7)	289	62 (7.2)	-0.5 (-1.4, 0.4)	-0.5 (-1.4, 0.4)	-0.5 (-1.4, 0.3)	969	-0.5 (-1.3, 0.3)
stunted at 18 mo	Systolic BP	690	97.2 (9.2)	289	96.6 (9.3)	-0.5 (-1.9, 0.9)	-0.5 (-1.9, 0.8)	-1 (-2.3, 0.3)	969	-0.9 (-2.2, 0.3)
stunted at 18 mo	**HAZ**	**691**	**-0.2 (0.7)**	**290**	**-1.3 (0.6)**	**-1.1 (-1.2, -1)**	**-1.1 (-1.2, -1)**	**-1.1 (-1.2, -1)**	971	**-1.1 (-1.2, -1)**
stunted at 18 mo	**WAZ**	**690**	**-0.4 (0.8)**	**289**	**-1.3 (0.7)**	**-0.9 (-1, -0.8)**	**-0.9 (-1, -0.8)**	**-0.9 (-1, -0.7)**	969	**-0.9 (-1, -0.7)**
stunted at 18 mo	**BMI**	**690**	**-0.5 (0.8)**	**289**	**-0.7 (0.8)**	**-0.2 (-0.3, -0.1)**	**-0.2 (-0.3, -0.1)**	**-0.2 (-0.3, -0.1)**	969	**-0.2 (-0.3, -0.1)**
stunted at 18 mo	**Knee-heel**	**691**	**38 (1.7)**	**289**	**35.9 (1.6)**	**-2.1 (-2.3, -1.9)**	**-2.1 (-2.3, -1.9)**	**-2.2 (-2.4, -2)**	970	**-2.1 (-2.3, -1.9)**
stunted at 18 mo	**Head circ**	**691**	**51.5 (1.4)**	**290**	**50.9 (1.5)**	**-0.6 (-0.8, -0.4)**	**-0.6 (-0.7, -0.4)**	**-0.7 (-0.9, -0.5)**	971	**-0.7 (-0.9, -0.5)**

Early-life Exposure	Outcome	Not stunted at 18 months		Stunted at 18 months		GEE Mean difference (95% CI)				
Stunted at 18 months (LAZ < -2)		N1	Mean (SD)	N2	Mean (SD)	Unadjusted	Model 1 (arm)	Model 2	N for model3	Model 3
stunted at 18 mo	**MUAC**	**690**	**17.1 (1.3)**	**290**	**16.5 (1.1)**	**-0.7 (-0.8, -0.5)**	**-0.7 (-0.8, -0.5)**	**-0.6 (-0.8, -0.5)**	970	**-0.6 (-0.8, -0.4)**
stunted at 18 mo	**Waist circ**	**690**	**54.5 (3.1)**	**290**	**52.9 (2.8)**	**-1.6 (-2.1, -1.2)**	**-1.6 (-2.1, -1.2)**	**-1.7 (-2.2, -1.3)**	970	**-1.7 (-2.2, -1.3)**
stunted at 18 mo	**Hip circ**	**691**	**61.7 (4)**	**290**	**59 (3.1)**	**-2.7 (-3.2, -2.2)**	**-2.7 (-3.2, -2.2)**	**-2.6 (-3.1, -2.2)**	971	**-2.6 (-3.1, -2.1)**
stunted at 18 mo	**Calf circ**	**690**	**23.8 (1.7)**	**290**	**22.6 (1.4)**	**-1.1 (-1.4, -0.9)**	**-1.1 (-1.4, -0.9)**	**-1.1 (-1.3, -0.9)**	970	**-1.1 (-1.3, -0.9)**
stunted at 18 mo	**LMI**	683	12.2 (1.3)	290	12 (1.3)	-0.2 (-0.3, 0)	-0.2 (-0.3, 0)	-0.2 (-0.3, 0)	963	-0.2 (-0.3, 0)
stunted at 18 mo	**Imp Index**	**683**	**1.8 (0.3)**	**290**	**1.6 (0.2)**	**-0.2 (-0.2, -0.2)**	**-0.2 (-0.2, -0.2)**	**-0.2 (-0.2, -0.2)**	963	**-0.2 (-0.2, -0.2)**
stunted at 18 mo	Phase angle	683	5 (0.5)	290	4.9 (0.6)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0)	963	0 (-0.1, 0)
stunted at 18 mo	**Total SFT**	**688**	**27.7 (6.4)**	**290**	**25.7 (5.5)**	**-2 (-2.9, -1.1)**	**-2 (-2.9, -1)**	**-1.6 (-2.5, -0.7)**	969	**-1.6 (-2.5, -0.7)**
stunted at 18 mo	**Peripheral SFT**	**689**	**16.6 (3.8)**	**290**	**15.3 (3.3)**	**-1.3 (-1.9, -0.8)**	**-1.3 (-1.9, -0.8)**	**-1 (-1.6, -0.5)**	969	**-1 (-1.6, -0.5)**
stunted at 18 mo	**Central SFT**	**690**	**11.2 (3.2)**	**290**	**10.5 (2.6)**	**-0.7 (-1.2, -0.3)**	**-0.7 (-1.2, -0.3)**	**-0.6 (-1, -0.2)**	971	**-0.6 (-1, -0.2)**
stunted at 18 mo	Hb	691	12.7 (1.2)	290	12.6 (1.3)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.1)	971	0 (-0.2, 0.1)

Table A5-8 Associations of Stunted children at 18 months (LAZ <-2) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

A5-4 Early-life Head circumference on 7-year SAHARAN Toolbox outcomes

Early-life exposure: Head Circumference at 3 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
Head Circ Z at 3 mo	MPI	**620**	**1 (0, 2)**	**1 (0, 2)**	**1 (0, 2)**	**609**	**1 (0, 1)**	**0.09**	**0.08**
Head Circ Z at 3 mo	SAT	624	2 (0, 4)	2 (0, 4)	2 (0, 4)	**609**	**2 (0, 4)**	**0.06**	**0.07**
Head Circ Z at 3 mo	Plus EF	**611**	**3 (1, 4)**	**3 (1, 4)**	**2 (1, 4)**	**600**	**2 (0, 4)**	**0.10**	**0.09**
Head Circ Z at 3 mo	Fine motor	618	**-0.7 (-1.2, -0.1)**	**-0.7 (-1.2, -0.1)**	**-0.6 (-1.1, 0)**	**609**	**-0.5 (-1, 0)**	**-0.10**	**-0.09**
Head Circ Z at 3 mo	SDQ	624	0 (-1, 0)	0 (-1, 0)	0 (-1, 0)	**608**	**0 (-1, 0)**	**-0.04**	**-0.05**
Head Circ Z at 3 mo	Child Socioem	609	0 (0, 0)	0 (0, 0)	0 (0, 0)	**598**	**0 (0, 0)**	0.10	**0.09**
Head Circ Z at 3 mo	Grip strength	**621**	**0.2 (0.1, 0.4)**	**0.2 (0.1, 0.4)**	**0.3 (0.2, 0.4)**	**609**	**0.2 (0.1, 0.4)**	**0.13**	**0.14**
Head Circ Z at 3 mo	Broad jump	619	0.8 (-0.2, 1.8)	0.8 (-0.1, 1.8)	1.3 (0.4, 2.1)	**608**	**1 (0.1, 1.9)**	**0.05**	**0.08**
Head Circ Z at 3 mo	Shuttle run	619	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	0 (-0.2, 0.2)	**607**	**0 (-0.2, 0.2)**	**0.04**	**0.00**
Head Circ Z at 3 mo	Diastolic BP	624	-0.2 (-0.9, 0.4)	-0.2 (-0.9, 0.4)	0 (-0.6, 0.6)	**608**	**0 (-0.6, 0.7)**	**-0.04**	**0.00**
Head Circ Z at 3 mo	Systolic BP	624	-0.4 (-1, 0.2)	-0.4 (-1, 0.2)	-0.1 (-0.7, 0.5)	**608**	**-0.1 (-0.7, 0.5)**	**-0.04**	**-0.01**
Head Circ Z at 3 mo	HAZ	**625**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**609**	**0.2 (0.1, 0.2)**	**0.22**	**0.21**
Head Circ Z at 3 mo	WAZ	**622**	**0.2 (0.1, 0.2)**	**0.2 (0.1, 0.2)**	**0.2 (0.1, 0.2)**	**608**	**0.2 (0.1, 0.2)**	**0.27**	**0.25**
Head Circ Z at 3 mo	BMI	**622**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	**608**	**0.1 (0.1, 0.2)**	**0.18**	**0.18**
Head Circ Z at 3 mo	Knee-heel	**625**	**0.3 (0.1, 0.4)**	**0.3 (0.1, 0.4)**	**0.3 (0.2, 0.5)**	**609**	**0.3 (0.2, 0.4)**	**0.14**	**0.17**
Head Circ Z at 3 mo	Head circ	**625**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**609**	**0.7 (0.6, 0.7)**	**0.46**	**0.49**
Head Circ Z at 3 mo	MUAC	**625**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**609**	**0.2 (0.1, 0.3)**	**0.14**	**0.13**
Head Circ Z at 3 mo	Waist circ	**625**	**0.5 (0.3, 0.7)**	**0.5 (0.3, 0.7)**	**0.6 (0.3, 0.8)**	**609**	**0.5 (0.3, 0.7)**	**0.17**	**0.18**
Head Circ Z at 3 mo	Hip circ	**625**	**0.6 (0.3, 0.9)**	**0.6 (0.3, 0.9)**	**0.7 (0.4, 1)**	**609**	**0.6 (0.4, 0.9)**	**0.16**	**0.18**
Head Circ Z at 3 mo	Calf circ	**625**	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.5)**	**609**	**0.3 (0.2, 0.4)**	**0.18**	**0.18**
Head Circ Z at 3 mo	LMI	**619**	**0.1 (0, 0.2)**	**0.1 (0, 0.2)**	**0.2 (0.1, 0.2)**	**605**	**0.2 (0.1, 0.2)**	**0.13**	**0.13**
Head Circ Z at 3 mo	Imp Index	**619**	**0 (0, 0.1)**	**0 (0, 0.1)**	**0.1 (0, 0.1)**	**605**	**0 (0, 0.1)**	**0.19**	**0.21**
Head Circ Z at 3 mo	Phase angle	620	0 (0, 0)	0 (0, 0)	0 (0, 0)	**606**	**0 (0, 0)**	**-0.02**	**0**
Head Circ Z at 3 mo	Total SFT	623	0.4 (0, 0.8)	0.4 (0, 0.8)	0.4 (0, 0.8)	**608**	**0.3 (-0.1, 0.7)**	**0.07**	**0.05**
Head Circ Z at 3 mo	Periphl SFT	**624**	**0.3 (0.1, 0.5)**	**0.3 (0.1, 0.5)**	**0.3 (0, 0.5)**	**608**	**0.2 (0, 0.5)**	**0.09**	**0.07**
Head Circ Z at 3 mo	Central SFT	624	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	**609**	**0.1 (-0.1, 0.3)**	**0.04**	**0.03**
Head Circ Z at 3 mo	Hb	625	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	**609**	**0 (-0.1, 0.1)**	**-0.02**	**-0.02**

Table A5-9 Associations of head circumference at 3 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 Ohms^{-1}, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

Associations of head circumference at 18 months with SAHARAN Toolbox Outcomes

Early-life exposure: Head circ- Z-score at 18 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
HCZ at 18 months	MPI	979	**2 (1, 3)**	**2 (1, 3)**	**2 (1, 3)**	969	**2 (1, 3)**	**0.18**	**0.17**
HCZ at 18 months	SAT	979	**4 (2, 6)**	**4 (2, 6)**	**4 (2, 5)**	969	**4 (2, 5)**	**0.14**	**0.14**
HCZ at 18 months	Plus EF	967	**3 (2, 5)**	**3 (2, 5)**	**3 (2, 5)**	957	**3 (2, 5)**	**0.14**	**0.14**
HCZ at 18 months	Fine motor	975	**-0.9 (-1.3, -0.4)**	**-0.9 (-1.4, -0.4)**	**-0.7 (-1.2, -0.3)**	965	**-0.8 (-1.2, -0.3)**	**-0.13**	**-0.12**
HCZ at 18 months	SDQ	978	0 (-1, 0)	0 (-1, 0)	0 (-1, 0)	968	0 (-1, 0)	-0.05	-0.05
HCZ at 18 months	Child Socioem	962	0 (0, 0)	0 (0, 0)	0 (0, 0)	952	0 (0, 0)	0.09	0.06
HCZ at 18 months	**Grip strength**	979	**0.3 (0.1, 0.4)**	**0.3 (0.1, 0.4)**	**0.3 (0.2, 0.4)**	969	**0.3 (0.1, 0.4)**	**0.14**	**0.14**
HCZ at 18 months	Broad jump	976	0.2 (-0.8, 1.1)	0.2 (-0.7, 1.1)	0.5 (-0.5, 1.5)	966	0.5 (-0.5, 1.4)	0.01	0.03
HCZ at 18 months	Shuttle run	976	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	-0.1 (-0.2, 0.1)	965	-0.1 (-0.2, 0.1)	0.02	-0.03
HCZ at 18 months	Diastolic BP	977	0.2 (-0.2, 0.7)	0.2 (-0.2, 0.7)	0.4 (0, 0.8)	967	0.4 (0, 0.9)	0.03	0.06
HCZ at 18 months	Systolic BP	977	-0.2 (-0.7, 0.4)	-0.2 (-0.7, 0.3)	0.2 (-0.3, 0.7)	967	0.2 (-0.3, 0.7)	-0.02	0.02
HCZ at 18 months	HAZ	979	**0.2 (0.2, 0.3)**	**0.2 (0.2, 0.3)**	**0.2 (0.2, 0.3)**	969	**0.2 (0.2, 0.3)**	**0.26**	**0.25**
HCZ at 18 months	WAZ	977	**0.3 (0.3, 0.4)**	**0.3 (0.3, 0.4)**	**0.3 (0.3, 0.4)**	967	**0.3 (0.3, 0.4)**	**0.37**	**0.37**
HCZ at 18 months	BMI	977	**0.2 (0.2, 0.3)**	**0.2 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	967	**0.2 (0.2, 0.3)**	**0.29**	**0.3**
HCZ at 18 months	Knee-heel	978	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.6)**	968	**0.4 (0.3, 0.5)**	**0.2**	**0.22**
HCZ at 18 months	Head circ	979	**1.0 (0.9, 1.1)**	**1.0 (0.9, 1.1)**	**1.1 (1, 1.1)**	969	**1.1 (1, 1.1)**	**0.69**	**0.72**
HCZ at 18 months	MUAC	978	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.4)**	968	**0.3 (0.2, 0.4)**	**0.2**	**0.21**
HCZ at 18 months	Waist circ	978	**0.8 (0.6, 1)**	**0.8 (0.6, 1)**	**0.9 (0.7, 1.1)**	968	**0.8 (0.6, 1)**	**0.26**	**0.27**
HCZ at 18 months	Hip circ	979	**0.9 (0.6, 1.2)**	**0.9 (0.6, 1.2)**	**1.0 (0.7, 1.2)**	969	**1 (0.7, 1.2)**	**0.23**	**0.25**
HCZ at 18 months	Calf circ	978	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.6)**	968	**0.4 (0.3, 0.5)**	**0.24**	**0.26**
HCZ at 18 months	LMI	971	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	**0.2 (0.1, 0.3)**	961	**0.2 (0.1, 0.3)**	**0.13**	**0.16**

Early-life exposure: Head circ- Z-score at 18 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
HCZ at 18 months	Imp Index	971	**0.1 (0, 0.1)**	**0.1 (0, 0.1)**	**0.1 (0.1, 0.1)**	961	**0.1 (0.1, 0.1)**	**0.23**	**0.26**
HCZ at 18 months	Phase angle	971	0 (-0.1, 0.0)	0.0 (-0.1, 0.0)	0.0 (-0.1, 0.0)	961	0 (-0.1, 0)	-0.06	-0.05
HCZ at 18 months	Total SFT	976	**0.8 (0.3, 1.3)**	**0.8 (0.3, 1.3)**	**0.8 (0.4, 1.3)**	967	**0.8 (0.4, 1.3)**	**0.13**	**0.14**
HCZ at 18 months	Periphl SFT	977	**0.6 (0.3, 0.8)**	**0.6 (0.3, 0.8)**	**0.5 (0.2, 0.8)**	967	**0.5 (0.2, 0.8)**	**0.15**	**0.14**
HCZ at 18 months	Central SFT	978	**0.3 (0.1, 0.5)**	**0.3 (0.1, 0.6)**	**0.4 (0.1, 0.6)**	969	**0.4 (0.1, 0.6)**	**0.1**	**0.12**
HCZ at 18 months	Hb	979	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (0, 0.1)	969	0 (0, 0.1)	0.01	0.03

Table A5-10 Associations of head circumference-for-age Z-score (HCZ) at 18 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

A5-5 Early-life Weight on 7 year SAHARAN Toolbox Outcomes

Early-life exposure: Birthweight	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
birthweight, Kg	MPI	945	1 (-1, 2)	1 (-1, 2)	1 (-1, 2)	929	0 (-1, 2)	0.02	0.01
birthweight, Kg	SAT	945	0 (-4, 3)	0 (-4, 3)	1 (-2, 4)	929	-1 (-5, 2)	-0.01	-0.02
birthweight, Kg	Plus EF	933	1 (-3, 4)	1 (-3, 4)	1 (-2, 5)	917	0 (-4, 3)	0.01	0.00
birthweight, Kg	Fine motor	941	0 (-0.9, 0.8)	-0.1 (-0.9, 0.8)	-0.4 (-1.3, 0.4)	925	-0.4 (-1.3, 0.5)	0.00	-0.03
birthweight, Kg	SDQ	944	0 (0, 1)	0 (0, 1)	0 (0, 1)	928	0 (-1, 1)	0.01	0.00
birthweight, Kg	Child Socioem	929	0 (0, 0)	0 (0, 0)	0 (0, 0)	913	0 (0, 0)	0.10	0.11
birthweight, Kg	Grip strength	945	0.5 (0.2, 0.8)	0.5 (0.2, 0.8)	0.4 (0.2, 0.7)	929	0.0 (-0.3, 0.3)	0.13	0.00
birthweight, Kg	Broad jump	942	1.8 (-0.4, 4.0)	1.8 (-0.4, 4.0)	1.6 (-0.5, 3.7)	926	-0.1 (-2.2, 2.0)	0.05	0.00
birthweight, Kg	Shuttle run	941	0.1 (-0.2, 0.5)	0.1 (-0.2, 0.5)	0.1 (-0.2, 0.5)	925	0.0 (-0.3, 0.4)	0.02	0.01
birthweight, Kg	Diastolic BP	943	0.4 (-0.7, 1.4)	0.4 (-0.7, 1.4)	0.1 (-1.0, 1.2)	927	-0.4 (-1.6, 0.7)	0.02	-0.03
birthweight, Kg	Systolic BP	943	1.7 (0.3, 3.1)	1.7 (0.3, 3.1)	1.4 (0.1, 2.7)	927	0.7 (-0.6, 1.9)	0.09	0.04
birthweight, Kg	**HAZ**	945	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	929	0.1 (0, 0.2)	0.26	0.06
birthweight, Kg	**WAZ**	943	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	927	0.2 (0.1, 0.3)	0.29	0.12
birthweight, Kg	BMI	943	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.4)**	927	0.2 (0.1, 0.3)	0.17	0.12
birthweight, Kg	**Knee-heel**	944	**1.1 (0.8, 1.3)**	**1.1 (0.8, 1.3)**	**1.1 (0.9, 1.3)**	928	0.3 (0.2, 0.5)	0.26	0.08
birthweight, Kg	**Head circ**	945	**0.6 (0.4, 0.8)**	**0.6 (0.4, 0.9)**	**0.6 (0.4, 0.8)**	929	0.4 (0.2, 0.6)	0.2	0.12
birthweight, Kg	**MUAC**	944	**0.5 (0.3, 0.6)**	**0.5 (0.3, 0.6)**	**0.5 (0.3, 0.6)**	928	0.2 (0.1, 0.4)	0.17	0.08
birthweight, Kg	**Waist circ**	944	**1.3 (0.9, 1.7)**	**1.3 (0.9, 1.7)**	**1.3 (0.9, 1.6)**	928	0.6 (0.3, 1.0)	0.20	0.10
birthweight, Kg	**Hip circ**	945	**1.7 (1.3, 2.2)**	**1.7 (1.3, 2.1)**	**1.8 (1.4, 2.2)**	929	0.7 (0.3, 1.1)	0.20	0.08
birthweight, Kg	**Calf circ**	944	**0.9 (0.6, 1.1)**	**0.9 (0.6, 1.1)**	**0.9 (0.7, 1.1)**	928	0.5 (0.3, 0.7)	0.24	0.14
birthweight, Kg	LMI	938	**0.5 (0.3, 0.7)**	**0.5 (0.3, 0.7)**	**0.4 (0.2, 0.5)**	922	0.3 (0.2, 0.5)	0.18	0.11
birthweight, Kg	**Imp Index**	938	**0.2 (0.1, 0.2)**	**0.2 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	922	0.1 (0.0, 0.1)	0.28	0.11
birthweight, Kg	Phase angle	937	-0.1 (-0.1, 0.0)	-0.1 (-0.1, 0.0)	-0.1 (-0.1, 0.0)	921	-0.1 (-0.2, 0.0)	-0.05	-0.09
birthweight, Kg	**Total SFT**	**942**	**1.2 (0.4, 2.1)**	**1.2 (0.4, 2.1)**	**1.6 (0.9, 2.3)**	927	0.9 (0.3, 1.6)	0.09	0.07
birthweight, Kg	**Periphl SFT**	943	**1.0 (0.5, 1.5)**	**1.0 (0.5, 1.5)**	**1.2 (0.8, 1.7)**	927	0.9 (0.4, 1.3)	0.12	0.11
birthweight, Kg	Central SFT	944	0.3 (-0.1, 0.7)	0.3 (-0.1, 0.7)	0.5 (0.1, 0.8)	929	0.1 (-0.2, 0.5)	0.05	0.02
birthweight, Kg	Hb	945	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	929	0.1 (-0.1, 0.3)	0.02	0.03

Table A5-11 Associations of Birthweight with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, length fo age Z-score at 18 months, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

A5-6 Directed Acyclic Graph of birthweight on 7 year SAHARAN Toolbox Outcomes

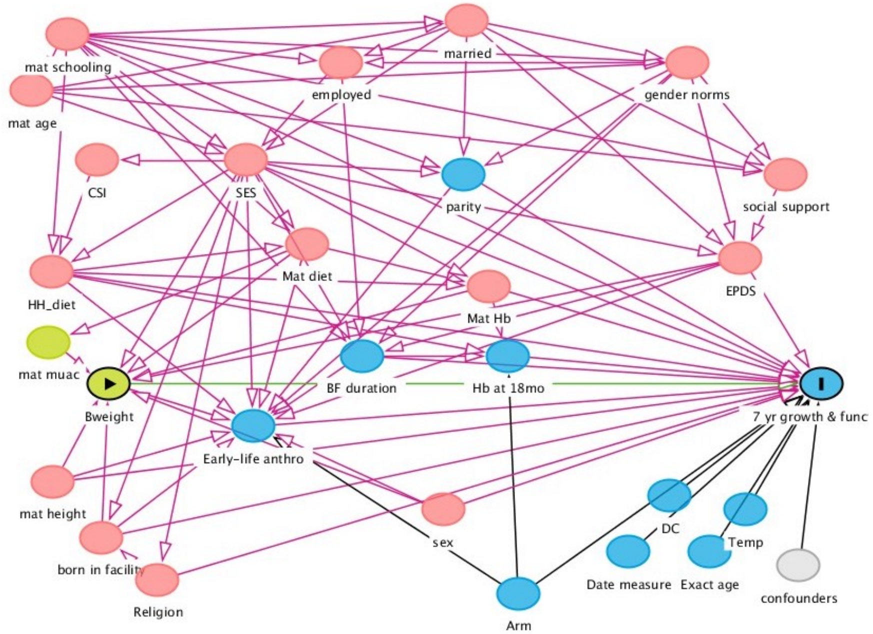


Figure A5-2 Directed acyclic graph for birthweight's effect on 7 year growth and function with early-life covariates.

Hence the model exploring the effect of early-life anthropometry on 7 year growth and function included the following co-variates arm, sex, data collector, ambient temperature, date measured, breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height, maternal schooling. Note that early-life anthropometry used length for age Z-score at 18 months.

Associations of Low Birthweight (<2500g) with SAHARAN Toolbox Outcomes

Early-life Exposure	Outcome	Not low birthweight		Low birthweight (LBW)		GEE Mean difference (95% CI)				
Low birthweight		N1	Mean (SD)	N2	Mean (SD)	Unadjusted	Model 1	Model 2	N 3	Model 3
LBW	MPI	858	49 (11)	87	47 (10)	-2 (-4, 0)	-2 (-4, 0)	-1 (-4, 1)	929	-1 (-3, 2)
LBW	SAT	858	47 (28)	87	44 (28)	-3 (-9, 2)	-3 (-9, 2)	-5 (-11, 0)	929	-3 (-8, 2)
LBW	Plus EF	846	115 (24)	87	114 (24)	-1 (-7, 4)	-1 (-7, 4)	-2 (-8, 3)	917	-1 (-5, 4)
LBW	Fine motor	854	23.9 (6.5)	87	24.6 (7.2)	0.8 (-0.7, 2.3)	0.8 (-0.7, 2.4)	1.2 (-0.3, 2.6)	925	1.2 (-0.4, 2.7)
LBW	SDQ	857	9 (5)	87	9 (5)	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	928	0 (-1, 1)
LBW	Child socioem	844	4 (1)	85	3 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	913	0 (0, 0)
LBW	Grip strength	858	10.7 (1.9)	87	10.3 (1.9)	-0.5 (-1, 0.1)	-0.4 (-1, 0.1)	-0.6 (-1.1, -0.1)	929	-0.1 (-0.5, 0.3)
LBW	**Broad jump**	**855**	**113.3 (15.3)**	**87**	**107.7 (13.3)**	**-5.6 (-8.9, -2.3)**	**-5.6 (-8.9, -2.4)**	**-5.6 (-8.7, -2.6)**	**926**	**-3.7 (-6.6, -0.8)**
LBW	Shuttle run	854	50.9 (2.7)	87	50.5 (2.5)	-0.4 (-1, 0.1)	-0.4 (-1, 0.1)	-0.5 (-1, 0)	925	-0.4 (-0.9, 0.1)
LBW	Diastolic BP	856	62.3 (7.5)	87	62.5 (7.8)	0.2 (-1.5, 1.9)	0.3 (-1.4, 2.1)	0.5 (-1.1, 2.1)	927	1 (-0.6, 2.6)
LBW	Systolic BP	856	97.2 (9.3)	87	95 (10.4)	-2.1 (-4.3, 0.1)	-2 (-4.2, 0.2)	-1.5 (-3.6, 0.6)	927	-0.6 (-2.7, 1.5)
LBW	**HAZ**	**858**	**-0.4 (0.8)**	**87**	**-1 (0.8)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.7, -0.3)**	**929**	**-0.1 (-0.2, 0)**
LBW	**WAZ**	**856**	**-0.6 (0.8)**	**87**	**-1.1 (0.8)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.7, -0.3)**	**-0.5 (-0.7, -0.3)**	**927**	**-0.1 (-0.3, 0)**
LBW	**BMI**	**856**	**-0.5 (0.9)**	**87**	**-0.7 (0.7)**	**-0.2 (-0.4, -0.1)**	**-0.3 (-0.4, -0.1)**	**-0.3 (-0.4, -0.1)**	**927**	**-0.1 (-0.3, 0)**
LBW	**Knee-heel**	**858**	**37.5 (1.9)**	**86**	**36.5 (1.7)**	**-0.9 (-1.3, -0.5)**	**-0.9 (-1.3, -0.5)**	**-1 (-1.4, -0.6)**	**928**	**-0.2 (-0.4, 0.1)**
LBW	**Head circ**	**858**	**51.3 (1.4)**	**87**	**50.8 (1.4)**	**-0.5 (-0.9, -0.2)**	**-0.5 (-0.9, -0.2)**	**-0.6 (-0.9, -0.3)**	**929**	**-0.3 (-0.6, -0.1)**
LBW	**MUAC**	**857**	**17 (1.3)**	**87**	**16.5 (1)**	**-0.5 (-0.8, -0.2)**	**-0.5 (-0.8, -0.2)**	**-0.5 (-0.8, -0.2)**	**928**	**-0.2 (-0.5, 0.1)**
LBW	**Waist circ**	**857**	**54.1 (3.1)**	**87**	**53.1 (2.6)**	**-1 (-1.8, -0.3)**	**-1 (-1.8, -0.3)**	**-1.2 (-1.8, -0.5)**	**928**	**-0.4 (-1, 0.3)**
LBW	**Hip circ**	**858**	**61 (4)**	**87**	**59.5 (3.2)**	**-1.5 (-2.2, -0.9)**	**-1.5 (-2.2, -0.9)**	**-1.7 (-2.3, -1)**	**929**	**-0.4 (-0.9, 0.2)**
LBW	**Calf circ**	**857**	**23.5 (1.7)**	**87**	**22.9 (1.7)**	**-0.6 (-1, -0.2)**	**-0.6 (-1, -0.2)**	**-0.6 (-1, -0.2)**	**928**	**-0.1 (-0.5, 0.3)**
LBW	**LMI**	**851**	**12.2 (1.3)**	**87**	**11.7 (1.3)**	**-0.5 (-0.8, -0.2)**	**-0.5 (-0.8, -0.2)**	**-0.4 (-0.6, -0.1)**	**922**	**-0.3 (-0.5, 0)**
LBW	**Imp Index**	**851**	**1.8 (0.3)**	**87**	**1.6 (0.2)**	**-0.1 (-0.2, -0.1)**	**-0.1 (-0.2, -0.1)**	**-0.1 (-0.2, -0.1)**	**922**	**0 (-0.1, 0)**
LBW	Phase angle	852	4.9 (0.5)	85	4.9 (0.6)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	921	0 (-0.1, 0.1)
LBW	Total SFT	855	27.1 (6.3)	87	26.7 (5.2)	-0.5 (-1.6, 0.7)	-0.5 (-1.6, 0.7)	-0.5 (-1.7, 0.6)	927	0.2 (-1, 1.5)
LBW	Peripheral SFT	856	16.2 (3.8)	87	15.8 (3.1)	-0.4 (-1.1, 0.3)	-0.4 (-1.1, 0.3)	-0.5 (-1.2, 0.2)	927	0 (-0.8, 0.7)
LBW	Central SFT	857	10.9 (3.1)	87	10.8 (2.6)	-0.1 (-0.7, 0.4)	-0.1 (-0.7, 0.4)	-0.1 (-0.6, 0.4)	929	0.3 (-0.3, 0.9)
LBW	Hb	858	12.7 (1.2)	87	12.6 (1.4)	-0.1 (-0.4, 0.3)	-0.1 (-0.4, 0.3)	-0.1 (-0.4, 0.3)	929	-0.1 (-0.4, 0.3)

Table A5-12 Associations of Low Birthweight (Birthweight < 2500g, LBW) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

	Not underweight at 18 months (WAZ > -2)	Underweight at 18 months (WAZ< -2)	Total	Relative risk (95% CI)	P-value
Birthweight > 2.5Kg	**789 (92.3%)**	**62 (75.6%)**	**851**		
Low birthweight (< 2.5 Kg)	**66 (7.7%)**	**20 (25.4%)**	**86**	**3.1 (2.5, 3.8)**	**P<0.001**
Total	**855**	**82**	**937**		

Table A5-13 Comparison of low birthweight and underweight at 18 months

	Not underweight at 18 months (WAZ > -2)	Underweight at 18 months (WAZ< -2)	Total	Relative risk (95% CI)	P-value
1 mo WAZ >-2	**447 (92.4%)**	**36 (70.6%)**	**483**		
Underweight at 1 mo (WAZ < -2)	**37 (7.6%)**	**15 (29.4%)**	**52**	**3.4 (2.6, 4.3)**	**P<0.001**
Total	**484**	**51**	**535**		

Table A5-14 Comparison of underweight at 1 month and underweight at 18 months

Associations of Weight-for-age (WAZ) at 18 months with SAHARAN Toolbox Outcomes

Early-life exposure:Weight-for-Age Z-score at 18 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised coefficient	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	Adjusted (Chord)
WAZ at 18 months	MPI	**981**	**1 (0, 2)**	**1 (0, 2)**	**1 (0, 2)**	**971**	**1 (0, 2)**	**0.11**	**0.10**
WAZ at 18 months	SAT	**981**	**3 (1, 5)**	**3 (1, 5)**	**3 (1, 4)**	**971**	**3 (1, 4)**	**0.11**	**0.09**
WAZ at 18 months	Plus EF	969	1 (0, 3)	1 (0, 3)	1 (0, 3)	**959**	**1 (0, 3)**	**0.06**	**0.05**
WAZ at 18 months	Fine motor	977	-0.5 (-1, -0.1)	-0.5 (-1, -0.1)	-0.4 (-0.8, 0)	**967**	**-0.4 (-0.8, 0)**	**-0.08**	**-0.06**
WAZ at 18 months	SDQ	980	0 (-1, 0)	0 (-1, 0)	0 (0, 0)	**970**	**0 (-1, 0)**	**-0.04**	**-0.03**
WAZ at 18 months	Child Socioem	964	0 (0, 0)	0 (0, 0)	0 (0, 0)	954	**0 (0, 0)**	0.02	**0.02**
WAZ at 18 months	**Grip strength**	**981**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.9)**	**971**	**0.7 (0.6, 0.8)**	**0.35**	**0.38**
WAZ at 18 months	**Broad jump**	**978**	**1.3 (0.5, 2.2)**	**1.3 (0.5, 2.2)**	**1.5 (0.7, 2.3)**	**968**	**1.5 (0.7, 2.3)**	**0.08**	**0.10**
WAZ at 18 months	Shuttle run	978	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.1)	**967**	**0 (-0.2, 0.1)**	**-0.01**	**-0.01**
WAZ at 18 months	Diastolic BP	**979**	**1.1 (0.6, 1.6)**	**1.1 (0.6, 1.6)**	**1 (0.5, 1.5)**	**969**	**1 (0.6, 1.5)**	**0.15**	**0.14**
WAZ at 18 months	Systolic BP	**979**	**1.3 (0.6, 1.9)**	**1.3 (0.6, 1.9)**	**1.4 (0.8, 2)**	**969**	**1.4 (0.8, 2)**	**0.14**	**0.15**
WAZ at 18 months	HAZ	**981**	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**971**	**0.5 (0.4, 0.5)**	**0.55**	**0.54**
WAZ at 18 months	WAZ	**979**	**0.6 (0.5, 0.6)**	**0.6 (0.5, 0.6)**	**0.6 (0.5, 0.6)**	**969**	**0.6 (0.5, 0.6)**	**0.67**	**0.67**
WAZ at 18 months	BMI	**979**	**0.4 (0.3, 0.4)**	**0.4 (0.3, 0.4)**	**0.4 (0.3, 0.4)**	**969**	**0.4 (0.3, 0.4)**	**0.46**	**0.46**
WAZ at 18 months	Knee-heel	**980**	**1 (0.8, 1.1)**	**1 (0.8, 1.1)**	**1 (0.9, 1.1)**	**970**	**1 (0.8, 1.1)**	**0.49**	**0.49**
WAZ at 18 months	Head circ	**981**	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	**0.5 (0.4, 0.6)**	**971**	**0.5 (0.4, 0.6)**	**0.27**	**0.33**
WAZ at 18 months	MUAC	**980**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**	**970**	**0.7 (0.6, 0.7)**	**0.52**	**0.51**
WAZ at 18 months	Waist circ	**980**	**1.5 (1.3, 1.7)**	**1.5 (1.3, 1.7)**	**1.5 (1.4, 1.7)**	**970**	**1.5 (1.3, 1.7)**	**0.48**	**0.49**
WAZ at 18 months	Hip circ	**981**	**2.2 (2, 2.5)**	**2.2 (2, 2.5)**	**2.2 (2, 2.4)**	**971**	**2.2 (2, 2.4)**	**0.56**	**0.55**
WAZ at 18 months	Calf circ	**980**	**0.9 (0.8, 1)**	**0.9 (0.8, 1)**	**0.9 (0.8, 1)**	**970**	**0.9 (0.8, 1)**	**0.56**	**0.56**
WAZ at 18 months	LMI	**973**	**0.4 (0.3, 0.4)**	**0.4 (0.3, 0.4)**	**0.4 (0.3, 0.5)**	**963**	**0.4 (0.3, 0.5)**	**0.28**	**0.31**
WAZ at 18 months	Imp Index	**973**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	**963**	**0.1 (0.1, 0.1)**	**0.51**	**0.53**
WAZ at 18 months	Phase angle	**973**	**0 (0, 0.1)**	**0 (0, 0.1)**	**0 (0, 0.1)**	**963**	**0 (0, 0.1)**	**0.06**	**0.06**
WAZ at 18 months	Total SFT	**978**	**2.4 (2, 2.8)**	**2.4 (2, 2.8)**	**2.2 (1.8, 2.6)**	**969**	**2.2 (1.8, 2.6)**	**0.39**	**0.36**
WAZ at 18 months	Periphl SFT	**979**	**1.5 (1.3, 1.7)**	**1.5 (1.3, 1.7)**	**1.4 (1.1, 1.6)**	**969**	**1.4 (1.1, 1.6)**	**0.4**	**0.37**
WAZ at 18 months	Central SFT	**980**	**1 (0.7, 1.3)**	**1 (0.7, 1.3)**	**0.9 (0.7, 1.2)**	**971**	**0.9 (0.7, 1.2)**	**0.32**	**0.30**
WAZ at 18 months	Hb	981	0.1 (0, 0.1)	0.1 (0, 0.1)	0.1 (0, 0.1)	**971**	**0.1 (0, 0.1)**	**0.05**	**0.07**

Table A5-15 Associations of Weight-for-age Z-score (WAZ) at 18 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

Associations of Underweight (WAZ <-2) at 18 months with SAHARAN Toolbox outcomes

Early-life Exposure: Underweight at 18 months (WAZ < -2)	Outcome	Not underweight at 18 months (WAZ > -2)		Underweight at 18 months (WAZ < -2)		GEE Mean difference (95% CI)				
		N1	Mean (SD)	N2	Mean (SD)	Unadjusted	Model 1 (arm)	Model 2	N adj	Model 3
UWT at 18 mo	MPI	895	48 (11)	86	47 (11)	-2 (-4, 1)	-2 (-4, 1)	-2 (-4, 1)	971	-1 (-4, 1)
UWT at 18 mo	SAT	895	46 (28)	86	41 (24)	-6 (-12, 0)	0 (0, 0)	-6 (-11, 0)	971	-5 (-11, 0)
UWT at 18 mo	Plus EF	883	115 (24)	86	114 (25)	0 (-6, 5)	-1 (-3, 1)	-1 (-7, 4)	959	-1 (-6, 5)
UWT at 18 mo	Fine motor	892	24 (6.6)	85	24.7 (6.5)	0.8 (-0.7, 2.3)	0.8 (-0.6, 2.3)	0.7 (-0.8, 2.1)	967	0.7 (-0.8, 2.1)
UWT at 18 mo	SDQ	894	9 (5)	86	8 (6)	0 (-2, 1)	0 (-2, 1)	0 (-2, 1)	970	0 (-2, 1)
UWT at 18 mo	Child socioem	879	4 (1)	85	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	954	0 (0, 0)
UWT at 18 mo	**Grip strength**	**895**	**10.8 (1.9)**	**86**	**9.6 (1.9)**	**-1.2 (-1.5, -0.8)**	**-1.1 (-1.5, -0.8)**	**-1.3 (-1.7, -0.9)**	**971**	**-1.3 (-1.7, -0.9)**
UWT at 18 mo	**Broad jump**	**893**	**113.1 (15.3)**	**85**	**110 (13.4)**	**-3.2 (-5.9, -0.4)**	**-3.2 (-6, -0.4)**	**-4.2 (-6.7, -1.6)**	**968**	**-4.1 (-6.7, -1.5)**
UWT at 18 mo	Shuttle run	893	50.9 (2.7)	85	50.6 (2.5)	-0.3 (-0.8, 0.3)	-0.3 (-0.8, 0.3)	-0.1 (-0.7, 0.4)	967	-0.2 (-0.7, 0.4)
UWT at 18 mo	**Diastolic BP**	**893**	**62.5 (7.6)**	**86**	**60.1 (6.7)**	**-2.5 (-4, -0.9)**	**-2.4 (-4, -0.9)**	**-2.3 (-3.8, -0.8)**	**969**	**-2.3 (-3.8, -0.8)**
UWT at 18 mo	**Systolic BP**	**893**	**97.2 (9.3)**	**86**	**95.4 (9.1)**	**-1.8 (-3.8, 0.2)**	**-1.8 (-3.8, 0.2)**	**-2 (-3.9, -0.1)**	**969**	**-2.1 (-4, -0.1)**
UWT at 18 mo	**HAZ**	**895**	**-0.4 (0.8)**	**86**	**-1.4 (0.7)**	**-1 (-1.2, -0.9)**	**-1 (-1.2, -0.9)**	**-1 (-1.2, -0.8)**	**971**	**-1 (-1.2, -0.8)**
UWT at 18 mo	**WAZ**	**893**	**-0.6 (0.8)**	**86**	**-1.6 (0.6)**	**-1.1 (-1.2, -1)**	**-1.1 (-1.2, -1)**	**-1.1 (-1.2, -0.9)**	**969**	**-1.1 (-1.2, -0.9)**
UWT at 18 mo	**BMI**	**893**	**-0.5 (0.8)**	**86**	**-1.1 (0.8)**	**-0.6 (-0.8, -0.4)**	**-0.6 (-0.8, -0.4)**	**-0.6 (-0.8, -0.4)**	**969**	**-0.6 (-0.8, -0.4)**
UWT at 18 mo	**Knee-heel**	**894**	**37.6 (1.9)**	**86**	**35.6 (1.6)**	**-2 (-2.4, -1.6)**	**-2 (-2.4, -1.6)**	**-2.1 (-2.4, -1.7)**	**970**	**-2 (-2.4, -1.6)**
UWT at 18 mo	**Head circ**	**895**	**51.4 (1.4)**	**86**	**50.5 (1.3)**	**-0.9 (-1.2, -0.6)**	**-0.9 (-1.2, -0.6)**	**-1.1 (-1.3, -0.8)**	**971**	**-1.1 (-1.3, -0.8)**
UWT at 18 mo	**MUAC**	**894**	**17 (1.3)**	**86**	**15.9 (1.0)**	**-1.1 (-1.3, -0.9)**	**-1.1 (-1.3, -0.9)**	**-1.1 (-1.3, -0.8)**	**970**	**-1 (-1.3, -0.8)**
UWT at 18 mo	**Waist circ**	**894**	**54.3 (3.1)**	**86**	**51.8 (2.9)**	**-2.4 (-3, -1.9)**	**-2.4 (-3, -1.9)**	**-2.5 (-3.1, -2)**	**970**	**-2.5 (-3.1, -1.9)**
UWT at 18 mo	**Hip circ**	**895**	**61.2 (3.9)**	**86**	**57.6 (2.7)**	**-3.6 (-4.3, -3)**	**-3.6 (-4.3, -3)**	**-3.6 (-4.3, -3)**	**971**	**-3.6 (-4.3, -2.9)**
UWT at 18 mo	**Calf circ**	**894**	**23.6 (1.7)**	**86**	**22.1 (1.2)**	**-1.4 (-1.7, -1.2)**	**-1.4 (-1.7, -1.2)**	**-1.4 (-1.7, -1.2)**	**970**	**-1.4 (-1.7, -1.1)**
UWT at 18 mo	**LMI**	**887**	**12.1 (1.3)**	**86**	**11.7 (1.3)**	**-0.4 (-0.7, -0.2)**	**-0.4 (-0.7, -0.2)**	**-0.5 (-0.7, -0.3)**	**963**	**-0.5 (-0.8, -0.3)**
UWT at 18 mo	**Imp Index**	**887**	**1.8 (0.3)**	**86**	**1.6 (0.2)**	**-0.2 (-0.3, -0.2)**	**-0.2 (-0.2, -0.2)**	**-0.2 (-0.3, -0.2)**	**963**	**-0.2 (-0.3, -0.2)**
UWT at 18 mo	Phase angle	887	5 (0.6)	86	4.9 (0.5)	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	963	-0.1 (-0.2, 0)
UWT at 18 mo	**Total SFT**	**892**	**27.4 (6.3)**	**86**	**24.2 (4.5)**	**-3.2 (-4.3, -2)**	**-3.2 (-4.4, -2)**	**-2.9 (-4, -1.8)**	**969**	**-2.8 (-3.9, -1.6)**
UWT at 18 mo	**Peripheral SFT**	**893**	**16.4 (3.8)**	**86**	**14.4 (2.8)**	**-2 (-2.7, -1.3)**	**-2 (-2.7, -1.3)**	**-1.8 (-2.5, -1.1)**	**969**	**-1.7 (-2.4, -1.1)**
UWT at 18 mo	**Central SFT**	**894**	**11.1 (3.1)**	**86**	**9.8 (2.2)**	**-1.2 (-1.8, -0.7)**	**-1.2 (-1.8, -0.7)**	**-1.1 (-1.7, -0.6)**	**971**	**-1 (-1.6, -0.5)**
UWT at 18 mo	Hb	895	12.7 (1.2)	86	12.4 (1.2)	-0.3 (-0.5, 0)	-0.3 (-0.5, 0)	-0.3 (-0.6, 0)	971	-0.3 (-0.6, 0)

Table A5-16 Associations of Underweight (WAZ<-2) at 18 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

A5-7 Early-life Mid-Upper Arm Circumference (MUAC) on SAHARAN Toolbox Outcomes

Associations of Mid-upper Arm Circumference Z-score (MUACZ) at 3 months with SAHARAN Toolbox outcomes

Early-life exposure: MUAC at 3 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
MUACZ at 3 mo	MPI	567	1 (0, 2)	1 (0, 2)	1 (0, 2)	557	1 (0, 2)	0.08	0.06
MUACZ at 3 mo	SAT	570	1 (-1, 4)	1 (-1, 4)	1 (-2, 4)	557	0 (-2, 3)	0.03	0.02
MUACZ at 3 mo	Plus EF	558	3 (1, 5)	3 (1, 5)	3 (1, 5)	548	2 (0, 5)	0.10	0.09
MUACZ at 3 mo	Fine motor	565	-0.5 (-1.2, 0.2)	-0.5 (-1.2, 0.2)	-0.5 (-1.2, 0.2)	557	-0.3 (-0.9, 0.3)	-0.04	-0.04
MUACZ at 3 mo	SDQ	569	0 (-1, 0)	0 (-1, 0)	0 (-1, 0)	556	0 (-1, 0)	-0.02	-0.03
MUACZ at 3 mo	Child Socioem	557	0 (0, 0)	0 (0, 0)	0 (0, 0)	548	0 (0, 0)	0.03	0.03
MUACZ at 3 mo	Grip strength	568	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	557	0.3 (0.1, 0.5)	0.12	0.13
MUACZ at 3 mo	Broad jump	566	0.1 (-1.5, 1.7)	0.2 (-1.4, 1.8)	0.2 (-1.2, 1.7)	556	-0.1 (-1.6, 1.4)	-0.01	-0.01
MUACZ at 3 mo	Shuttle run	565	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.3)	0.0 (-0.2, 0.3)	555	0.1 (-0.2, 0.3)	0.00	0.02
MUACZ at 3 mo	Diastolic BP	570	0.4 (-0.3, 1.1)	0.4 (-0.3, 1.1)	0.2 (-0.5, 0.9)	557	0.3 (-0.3, 1.0)	0.06	0.03
MUACZ at 3 mo	Systolic BP	570	0.8 (-0.1, 1.7)	0.8 (-0.1, 1.7)	0.5 (-0.3, 1.4)	557	0.4 (-0.4, 1.2)	0.08	0.06
MUACZ at 3 mo	HAZ	570	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.0, 0.2)	557	0.1 (0.0, 0.2)	0.14	0.13
MUACZ at 3 mo	WAZ	568	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	556	0.2 (0.2, 0.3)	0.25	0.24
MUACZ at 3 mo	BMI	568	0.2 (0.2, 0.3)	0.2 (0.1, 0.3)	0.2 (0.2, 0.3)	556	0.2 (0.2, 0.3)	0.24	0.24
MUACZ at 3 mo	Knee-heel	570	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	557	0.2 (0.1, 0.4)	0.12	0.11
MUACZ at 3 mo	Head circ	570	0.2 (0.1, 0.3)	0.2 (0.0, 0.3)	0.2 (0.1, 0.3)	557	0.2 (0.1, 0.3)	0.08	0.11
MUACZ at 3 mo	MUAC	570	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	557	0.4 (0.3, 0.5)	0.25	0.24
MUACZ at 3 mo	Waist circ	570	0.6 (0.3, 0.8)	0.6 (0.3, 0.8)	0.6 (0.4, 0.9)	557	0.6 (0.4, 0.9)	0.17	0.18
MUACZ at 3 mo	Hip circ	570	1.0 (0.7, 1.3)	1.0 (0.6, 1.3)	0.9 (0.6, 1.2)	557	0.9 (0.5, 1.2)	0.22	0.2
MUACZ at 3 mo	Calf circ	570	0.5 (0.3, 0.6)	0.5 (0.3, 0.6)	0.5 (0.3, 0.6)	557	0.5 (0.4, 0.6)	0.26	0.26
MUACZ at 3 mo	LMI	566	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.3 (0.3, 0.4)	554	0.3 (0.3, 0.4)	0.25	0.24
MUACZ at 3 mo	Imp Index	566	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	554	0.1 (0.1, 0.1)	0.26	0.25
MUACZ at 3 mo	Phase angle	566	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (0.0, 0.1)	554	0.0 (0.0, 0.1)	0.00	0.00
MUACZ at 3 mo	Total SFT	568	1.4 (0.9, 2.0)	1.4 (0.9, 2.0)	1.3 (0.8, 1.9)	556	1.2 (0.7, 1.8)	0.21	0.19
MUACZ at 3 mo	Periphl SFT	569	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)	556	0.9 (0.5, 1.2)	0.25	0.22
MUACZ at 3 mo	Central SFT	569	0.4 (0.1, 0.7)	0.4 (0.1, 0.7)	0.4 (0.1, 0.7)	557	0.3 (0.0, 0.5)	0.11	0.10

Early-life exposure: MUAC at 3 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
MUACZ at 3 mo	Hb	570	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	**557**	**0.1 (0.0, 0.2)**	**0.08**	**0.10**

Table A5-17 Associations of Mid-upper arm circumference Z-score (MUACZ) at 3 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

Associations of Mid-upper Arm Circumference Z-score (MUACZ) at 18 months with SAHARAN Toolbox outcomes

Early-life exposure: MUAC-for-Age Z-score at 18 months	Early-life Outcomes	GEE Mean difference (95% CI)						Standardised coefficient (Chord)	
		n	Unadjusted	Model 1	Model 2	n	Model 3	unadjusted	adjusted
MUACZ at 18 months	MPI	980	1 (0, 2)	1 (0, 2)	1 (0, 2)	**970**	**1 (0, 2)**	**0.08**	**0.06**
MUACZ at 18 months	SAT	980	2 (0, 4)	2 (0, 4)	2 (0, 4)	**970**	**2 (0, 3)**	**0.07**	**0.05**
MUACZ at 18 months	Plus EF	968	**2 (0, 4)**	**2 (0, 4)**	**2 (0, 4)**	**958**	**2 (0, 4)**	**0.07**	**0.07**
MUACZ at 18 months	Fine motor	976	**-0.6 (-1.1, -0.1)**	**-0.6 (-1.1, -0.1)**	**-0.5 (-0.9, -0.1)**	**966**	**-0.5 (-0.9, -0.1)**	**-0.08**	**-0.07**
MUACZ at 18 months	SDQ	979	0 (-1, 0)	0 (-1, 0)	0 (-1, 0)	**969**	**0 (-1, 0)**	**-0.03**	**-0.03**
MUACZ at 18 months	Child Socioem	963	0 (0, 0)	0 (0, 0)	0 (0, 0)	953	**0 (0, 0)**	0.01	**-0.01**
MUACZ at 18 months	**Grip strength**	980	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	**0.6 (0.4, 0.7)**	**970**	**0.6 (0.4, 0.7)**	**0.23**	**0.25**
MUACZ at 18 months	**Broad jump**	977	-0.1 (-1.1, 0.9)	-0.1 (-1.1, 0.9)	0.3 (-0.7, 1.3)	**967**	**0.3 (-0.7, 1.3)**	**-0.01**	**0.01**
MUACZ at 18 months	Shuttle run	977	0 (-0.3, 0.2)	0 (-0.3, 0.2)	-0.1 (-0.3, 0.1)	**966**	**-0.1 (-0.3, 0.1)**	**-0.01**	**-0.04**
MUACZ at 18 months	Diastolic BP	978	**0.9 (0.3, 1.4)**	**0.9 (0.3, 1.4)**	**0.8 (0.3, 1.3)**	**968**	**0.9 (0.4, 1.4)**	**0.10**	**0.10**
MUACZ at 18 months	Systolic BP	978	**0.9 (0.2, 1.5)**	**0.8 (0.2, 1.5)**	**1 (0.5, 1.6)**	**968**	**1.1 (0.5, 1.6)**	**0.08**	**0.10**
MUACZ at 18 months	HAZ	980	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	**0.3 (0.2, 0.3)**	**970**	**0.2 (0.2, 0.3)**	**0.25**	**0.24**
MUACZ at 18 months	WAZ	978	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**968**	**0.5 (0.4, 0.5)**	**0.48**	**0.48**
MUACZ at 18 months	BMI	978	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**0.5 (0.4, 0.5)**	**968**	**0.5 (0.4, 0.5)**	**0.46**	**0.47**
MUACZ at 18 months	Knee-heel	979	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.6)**	**0.5 (0.4, 0.7)**	**969**	**0.5 (0.4, 0.6)**	**0.22**	**0.23**
MUACZ at 18 months	Head circ	980	**0.3 (0.2, 0.4)**	**0.3 (0.2, 0.4)**	**0.4 (0.3, 0.5)**	**970**	**0.4 (0.3, 0.5)**	**0.18**	**0.21**
MUACZ at 18 months	MUAC	979	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**	**969**	**0.8 (0.7, 0.9)**	**0.5**	**0.51**
MUACZ at 18 months	Waist circ	979	**1.3 (1.0, 1.5)**	**1.3 (1.0, 1.5)**	**1.4 (1.1, 1.6)**	**969**	**1.3 (1.1, 1.6)**	**0.35**	**0.37**
MUACZ at 18 months	Hip circ	980	**2.0 (1.7, 2.3)**	**2.0 (1.7, 2.3)**	**2.0 (1.7, 2.3)**	**970**	**2.0 (1.7, 2.3)**	**0.43**	**0.44**
MUACZ at 18 months	Calf circ	979	**0.9 (0.8, 1.0)**	**0.9 (0.8, 1.0)**	**0.9 (0.8, 1.0)**	**969**	**0.9 (0.8, 1.0)**	**0.46**	**0.48**
MUACZ at 18 months	LMI	972	**0.4 (0.3, 0.5)**	**0.4 (0.3, 0.5)**	**0.5 (0.4, 0.5)**	**962**	**0.5 (0.4, 0.5)**	**0.27**	**0.31**
MUACZ at 18 months	Imp Index	972	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	**0.1 (0.1, 0.1)**	**962**	**0.1 (0.1, 0.1)**	**0.33**	**0.36**
MUACZ at 18 months	Phase angle	972	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.1 (0, 0.1)	**962**	**0.1 (0.0, 0.1)**	**0.08**	**0.08**
MUACZ at 18 months	Total SFT	977	**2.8 (2.3, 3.2)**	**2.8 (2.3, 3.2)**	**2.7 (2.3, 3.1)**	**968**	**2.7 (2.2, 3.1)**	**0.39**	**0.38**
MUACZ at 18 months	Periphl SFT	978	**1.7 (1.5, 2.0)**	**1.7 (1.5, 2.0)**	**1.6 (1.4, 1.9)**	**968**	**1.6 (1.4, 1.9)**	**0.4**	**0.38**
MUACZ at 18 months	Central SFT	979	**1.2 (0.8, 1.5)**	**1.2 (0.8, 1.5)**	**1.2 (0.9, 1.5)**	**970**	**1.2 (0.8, 1.5)**	**0.33**	**0.33**
MUACZ at 18 months	Hb	980	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	**970**	**0.0 (0.0, 0.1)**	**0.03**	**0.04**

Table A5-18 Associations of Mid-upper arm circumference Z-score (MUACZ) at 18 months with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}. Model 1: SHINE trial arm, Model 2:Trial factors: SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3 (Baseline factors): Trial factors breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal years of schooling.

A5-8 Associations of Catch-up growth in height and weight from 18 months to 7 years with SAHARAN Toolbox Outcomes

Associations with catch-up in Height for age Z-score (∆HAZ) between 18 months to 7 years and SAHARAN Outcomes

Catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Adjusted difference Model 3 (	n	Model 4 early	unadjusted	Adjusted m3 cont	Adjusted m4 early
∆HAZ	MPI	981	1 (0, 1)	1 (0, 1)	1 (0, 2)	970	0 (0, 0)	971	0 (0, 0)	0.03	0.05	0.05
∆HAZ	SAT	981	1 (-1, 3)	1 (-1, 3)	1 (-1, 3)	970	0 (0, 0)	971	0 (0, 0)	0.02	0.03	0.03
∆HAZ	Plus EF	969	0 (-2, 2)	0 (-2, 3)	0 (-2, 3)	958	0 (0, 0)	959	0 (0, 0)	0	0.01	0.01
∆HAZ	Fine motor	977	-0.8 (-1.4, -0.2)	-0.7 (-1.3, -0.1)	-0.9 (-1.4, -0.3)	966	-0.1 (-0.1, 0)	967	-0.1 (-0.1, 0)	-0.08	-0.09	-0.09
∆HAZ	SDQ	980	0 (0, 1)	0 (0, 1)	0 (0, 1)	970	0 (0, 0)	970	0 (0, 0)	0.03	0.03	0.03
∆HAZ	Child Socioem	964	0 (0, 0)	0 (0, 0)	0 (0, 0)	953	0 (0, 0)	954	0 (0, 0)	0.01	0.02	0.02
∆HAZ	Grip strength	981	0.2 (0, 0.4)	0.2 (0, 0.4)	0.2 (0, 0.3)	970	0.1 (0, 0.1)	971	0.1 (0, 0.1)	0.08	0.06	0.05
∆HAZ	Broad jump	978	1.4 (0.1, 2.6)	1.4 (0.1, 2.6)	0.9 (-0.3, 2.2)	967	0.8 (-0.5, 2.1)	968	0 (0, 0.1)	0.06	0.05	0.04
∆HAZ	Shuttle run	978	-0.3 (-0.5, 0)	-0.3 (-0.5, 0)	-0.2 (-0.5, 0)	966	-0.1 (-0.1, 0)	967	-0.1 (-0.1, 0)	-0.07	-0.06	-0.06
∆HAZ	Diastolic BP	979	0.5 (-0.1, 1)	0.5 (0, 1)	0.4 (-0.1, 0.9)	968	0 (0, 0.1)	969	0 (0, 0.1)	0.04	0.03	0.04
∆HAZ	Systolic BP	979	0.5 (-0.4, 1.3)	0.5 (-0.4, 1.4)	0.1 (-0.7, 1)	968	0 (-0.1, 0.1)	969	0 (-0.1, 0.1)	0.04	0	0.01
∆HAZ	HAZ	981	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	970	0.2 (0.1, 0.2)	971	0.2 (0.1, 0.2)	0.15	0.17	0.16
∆HAZ	WAZ	979	0.1 (0, 0.2)	0.1 (0, 0.2)	0.1 (0, 0.2)	968	0.1 (0, 0.1)	969	0.1 (0, 0.1)	0.06	0.08	0.08
∆HAZ	BMI	979	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	-0.1 (-0.1, 0)	968	0 (-0.1, 0)	969	0 (-0.1, 0)	-0.06	-0.05	-0.05
∆HAZ	Knee-heel	980	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	969	0.1 (0.1, 0.2)	970	0.1 (0.1, 0.2)	0.15	0.14	0.14
∆HAZ	Head circ	981	0 (-0.1, 0.1)	0 (-0.1, 0.2)	0 (-0.1, 0.1)	970	0 (-0.1, 0.1)	971	0 (-0.1, 0)	0.02	0	-0.01
∆HAZ	MUAC	980	0 (-0.1, 0.2)	0 (-0.1, 0.2)	0 (-0.1, 0.2)	969	0 (0, 0.1)	970	0 (0, 0.1)	0.02	0.02	0.03
∆HAZ	Waist circ	980	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	969	0 (0, 0.1)	970	0 (0, 0.1)	0.05	0.05	0.05
∆HAZ	Hip circ	981	0.3 (0, 0.7)	0.3 (0, 0.7)	0.3 (0, 0.7)	970	0.1 (0, 0.1)	971	0.1 (0, 0.1)	0.06	0.05	0.06
∆HAZ	Calf circ	980	0.1 (0, 0.3)	0.1 (0, 0.3)	0.1 (0, 0.3)	969	0 (0, 0.1)	970	0 (0, 0.1)	0.05	0.05	0.05
∆HAZ	LMI	973	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0 (-0.1, 0.1)	962	0 (-0.1, 0.1)	963	0 (-0.1, 0.1)	0.03	0.01	0.01
∆HAZ	Imp Index	973	0 (0, 0.1)	0 (0, 0.1)	0 (0, 0.1)	962	0.1 (0, 0.2)	963	0.1 (0, 0.2)	0.13	0.1	0.1
∆HAZ	Phase angle	973	0 (-0.1, 0)	0 (-0.1, 0)	0 (-0.1, 0)	962	0 (-0.1, 0)	963	0 (-0.1, 0)	-0.03	-0.04	-0.04
∆HAZ	Total SFT	978	0.2 (-0.4, 0.7)	0.2 (-0.4, 0.7)	0.3 (-0.3, 0.8)	968	0 (0, 0.1)	969	0 (0, 0.1)	0.02	0.03	0.03
∆HAZ	Periphl SFT	979	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)	968	0 (0, 0.1)	969	0 (0, 0.1)	0.02	0.04	0.04
∆HAZ	Central SFT	980	0 (-0.3, 0.3)	0 (-0.3, 0.3)	0 (-0.2, 0.3)	970	0 (0, 0.1)	971	0 (0, 0.1)	0	0.01	0.01
∆HAZ	Hb	981	0.1 (0, 0.2)	0.1 (0, 0.2)	0 (-0.1, 0.1)	970	0 (0, 0.1)	971	0 (0, 0.1)	0.04	0.03	0.03

Table A5-19 Associations of Catch-up in Height-for-age Z-score from 18 months to 7 years (Catch-up HAZ) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,. Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling.

Associations with catch-up in Weight for age Z-score (∆WAZ) between 18 months to 7 years and SAHARAN Outcomes

Catch-up in Weight Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Model 3 (cont)	n	Model 4 early	unadjusted	Adjusted m3	Adjusted m4 early
∆WAZ	MPI	979	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	968	0 (-1, 1)	969	0 (-1, 1)	0.01	0.01	0.02
∆WAZ	SAT	979	0 (-2, 3)	0 (-2, 3)	1 (-1, 3)	968	1 (-1, 2)	969	1 (-1, 3)	0.01	0.02	0.02
∆WAZ	Plus EF	967	1 (-1, 3)	1 (-1, 3)	1 (-1, 3)	956	1 (-1, 3)	957	1 (-1, 3)	0.03	0.03	0.03
∆WAZ	Fine motor	975	-0.4 (-1, 0.1)	-0.4 (-1, 0.1)	-0.6 (-1.2, -0.1)	964	-0.6 (-1.1, -0.1)	965	-0.6 (-1.2, -0.1)	-0.05	-0.07	-0.07
∆WAZ	SDQ	978	0 (0, 1)	0 (0, 1)	0 (0, 1)	968	0 (0, 1)	968	0 (0, 1)	0.05	0.05	0.04
∆WAZ	Child Socioem	962	0 (0, 0)	0 (0, 0)	0 (0, 0)	951	0 (0, 0)	952	0 (0, 0)	0.02	0.03	0.03
∆WAZ	Grip strength	979	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	968	0.2 (0.1, 0.4)	969	0.2 (0.1, 0.4)	0.11	0.09	0.09
∆WAZ	Broad jump	976	1.7 (0.6, 2.8)	1.7 (0.6, 2.8)	1.6 (0.4, 2.8)	965	1.6 (0.5, 2.8)	966	1.6 (0.5, 2.7)	0.08	0.05	0.08
∆WAZ	Shuttle run	976	0 (-0.2, 0.3)	0 (-0.2, 0.3)	0 (-0.2, 0.3)	964	0.1 (-0.2, 0.3)	965	0 (-0.2, 0.3)	0	0.02	0.01
∆WAZ	Diastolic BP	977	0.3 (-0.2, 0.9)	0.4 (-0.2, 0.9)	0.2 (-0.4, 0.7)	966	0.2 (-0.4, 0.7)	967	0.1 (-0.4, 0.7)	0.03	0.02	0.01
∆WAZ	Systolic BP	977	0.4 (-0.3, 1)	0.4 (-0.3, 1.1)	0.1 (-0.6, 0.8)	966	0.1 (-0.6, 0.8)	967	0.1 (-0.6, 0.8)	0.03	0.01	0.01
∆WAZ	HAZ	979	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	968	0.2 (0.1, 0.3)	969	0.2 (0.1, 0.3)	0.15	0.17	0.17
∆WAZ	WAZ	979	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	968	0.3 (0.2, 0.4)	969	0.3 (0.2, 0.4)	0.28	0.29	0.29
∆WAZ	BMI	979	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	968	0.3 (0.2, 0.4)	969	0.3 (0.2, 0.4)	0.27	0.27	0.27
∆WAZ	Knee-heel	978	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	967	0.4 (0.2, 0.6)	968	0.4 (0.2, 0.6)	0.16	0.16	0.16
∆WAZ	Head circ	979	0.1 (0, 0.2)	0.1 (0, 0.2)	0 (-0.1, 0.1)	968	0 (-0.1, 0.1)	969	0 (-0.1, 0.1)	0.05	0.01	0.01
∆WAZ	MUAC	978	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	0.3 (0.2, 0.4)	967	0.3 (0.2, 0.4)	968	0.3 (0.2, 0.4)	0.17	0.17	0.18
∆WAZ	Waist circ	978	0.9 (0.6, 1.1)	0.9 (0.6, 1.1)	0.8 (0.6, 1.1)	967	0.8 (0.6, 1.1)	968	0.8 (0.6, 1.1)	0.21	0.2	0.2
∆WAZ	Hip circ	979	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	1 (0.6, 1.3)	968	1 (0.6, 1.3)	969	1 (0.6, 1.3)	0.18	0.19	0.19
∆WAZ	Calf circ	978	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.3, 0.6)	967	0.4 (0.3, 0.6)	968	0.4 (0.3, 0.6)	0.18	0.19	0.19
∆WAZ	LMI	971	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	960	0.2 (0.1, 0.3)	961	0.2 (0.1, 0.3)	0.14	0.13	0.13

ΔWAZ	**Imp Index**	**971**	**0.1 (0, 0.1)**	**0.1 (0, 0.1)**	**0.1 (0, 0.1)**	**960**	**0.1 (0, 0.1)**	**961**	**0.1 (0, 0.1)**	**0.2**	**0.19**	**0.19**
ΔWAZ	**Phase angle**	**971**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.2)**	**0.1 (0.1, 0.1)**	**960**	**0.1 (0.1, 0.1)**	**961**	**0.1 (0.1, 0.1)**	**0.15**	**0.14**	**0.14**
ΔWAZ	**Total SFT**	**976**	**0.8 (0.2, 1.4)**	**0.8 (0.2, 1.4)**	**1.1 (0.5, 1.7)**	**966**	**1.1 (0.5, 1.6)**	**967**	**1.1 (0.5, 1.7)**	**0.1**	**0.13**	**0.14**
ΔWAZ	**Periphl SFT**	**977**	**0.3 (0, 0.7)**	**0.3 (0, 0.7)**	**0.5 (0.2, 0.8)**	**966**	**0.5 (0.2, 0.8)**	**967**	**0.5 (0.2, 0.9)**	**0.07**	**0.1**	**0.11**
ΔWAZ	**Central SFT**	**978**	**0.5 (0.2, 0.8)**	**0.5 (0.2, 0.8)**	**0.6 (0.3, 0.8)**	**968**	**0.6 (0.3, 0.8)**	**969**	**0.6 (0.3, 0.9)**	**0.12**	**0.14**	**0.14**
ΔWAZ	**Hb**	**979**	**0 (-0.1, 0.1)**	**0 (-0.1, 0.1)**	**0 (-0.1, 0.1)**	**968**	**0 (-0.1, 0.1)**	**969**	**0 (-0.1, 0.1)**	**-0.02**	**-0.02**	**-0.02**

Table A5-20 Associations of Catch-up in Weight-for-age Z-score from 18 months to 7 years (Catch-up WAZ) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,. Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling.

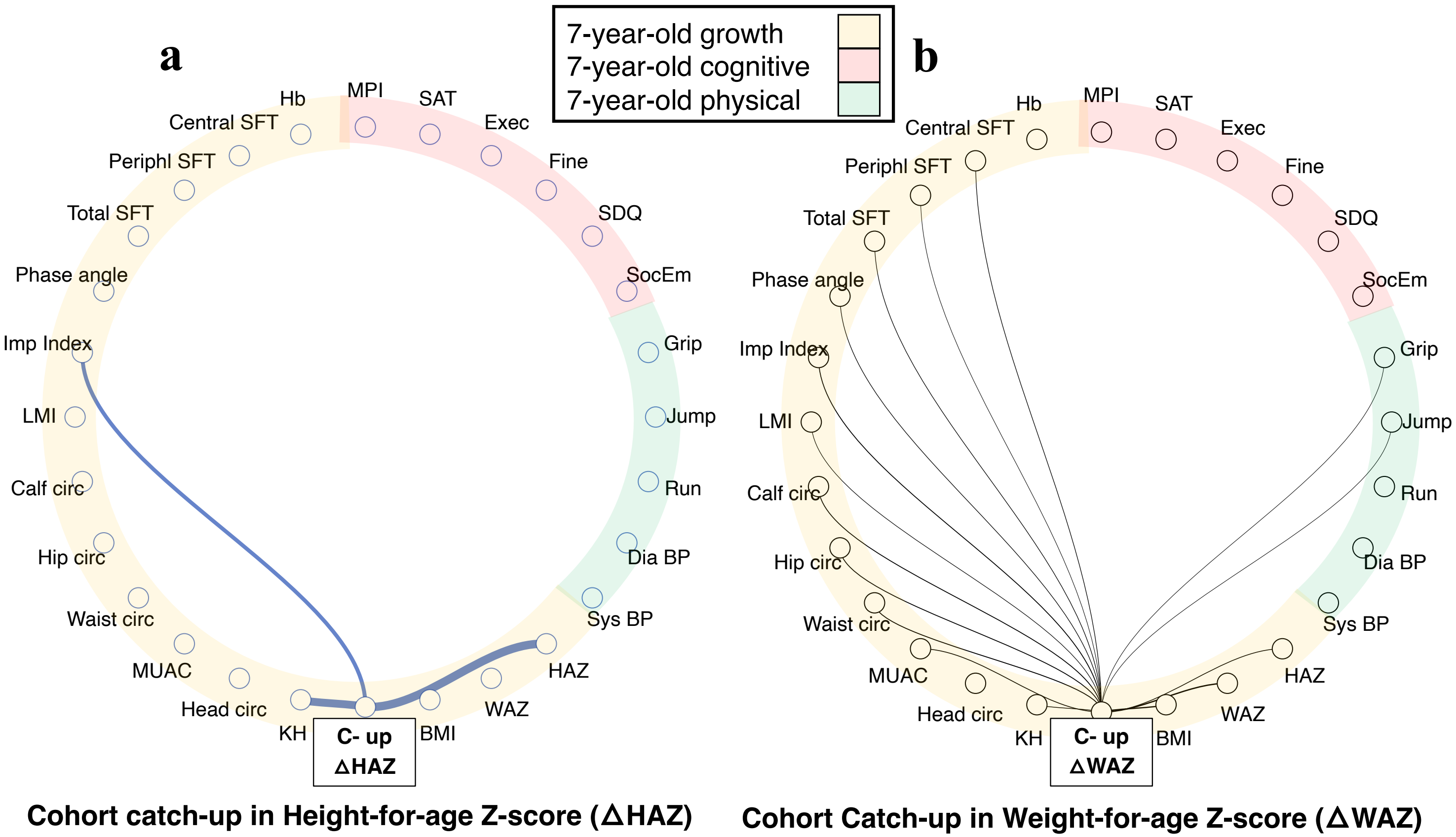


Figure A5-3 Associations of catch-up height-for-age Z-scores with 7-year growth, cognitive and physical function.

Clockwise from bottom: KH: Knee-heel length, Head circ: head circumference, MUAC: Mid-upper arm circumference, Waist circ: waist circumference, Hip circ: hip circumference, calf circ: calf circumference, LMI: Lean mass index, Total SFT: Total skinfold thickness, Periphl SFT: peripheral skinfold thickness, Central SFT: Central Skinfold thickness, Hb: Haemoglobin, MPI: Mental processing index (KABC-II total), SAT: School achievement test, Exec: Executive function (PlusEF total), Fine: Fine motor coordination, SDQ: Strength and difficulties questionnaire total (Socioemotional function), SocEM: Child's own socioemotional score, Grip: Grip strength, Jump: broadjump distance (leg strength), Run: Cardiovascular fitness (VO_2max from shuttle run test), Dia BP: Diastolic Blood pressure, Sys BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years. The relative width of the line is in proportion to the effect size for early-life growth as portrayed in chord diagrams for both contemporary and early-life growth.

Associations with catch-up in Height for age Z-score for Girls (F∆HAZ) between 18 months to 7 years and SAHARAN Toolbox Outcomes for the whole cohort

Girls' Catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Model 3 (	n	Model 4	unadjusted	Adjusted m3 cont	Adjusted m4 early
F∆HAZ	**MPI**	504	0 (-2, 2)	0 (-2, 2)	0 (-1, 2)	499	0 (-1, 2)	500	0 (-1, 2)	0	0.01	0.01
F∆HAZ	**SAT**	504	1 (-3, 4)	0 (-3, 4)	0 (-3, 3)	499	0 (-3, 3)	500	0 (-4, 4)	0.02	0	0
F∆HAZ	**Plus EF**	497	0 (-4, 4)	0 (-3, 4)	0 (-3, 4)	492	1 (-3, 5)	493	1 (-3, 5)	0	0.03	0.02
F∆HAZ	**Fine motor**	503	-0.8 (-1.8, 0.1)	-0.9 (-1.8, 0.1)	-0.8 (-1.7, 0.1)	498	-0.8 (-1.7, 0)	499	-0.9 (-1.8, 0.1)	-0.09	-0.09	-0.09
F∆HAZ	**SDQ**	503	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	499	0 (-1, 1)	499	0 (-1, 1)	-0.01	0.01	0
F∆HAZ	**Child Socioem**	498	0 (0, 0)	0 (0, 0)	0 (0, 0)	493	0 (0, 0)	494	0 (0, 0)	0	0.01	0.03
F∆HAZ	**Grip strength**	504	0.2 (-0.1, 0.4)	0.2 (-0.1, 0.4)	0.1 (-0.1, 0.4)	499	0.1 (-0.2, 0.4)	500	0.1 (-0.1, 0.4)	0.06	0.05	0.04
F∆HAZ	**Broad jump**	503	-0.2 (-2.2, 1.9)	-0.1 (-2.2, 1.9)	-0.8 (-2.7, 1.2)	498	-1.1 (-3, 0.8)	499	-0.6 (-2.6, 1.4)	-0.01	-0.07	-0.03
F∆HAZ	**Shuttle run**	502	-0.3 (-0.6, 0.1)	-0.2 (-0.6, 0.1)	-0.2 (-0.5, 0.1)	497	-0.2 (-0.5, 0.1)	498	-0.2 (-0.5, 0.1)	-0.07	-0.05	-0.05
F∆HAZ	**Diastolic BP**	504	0.4 (-0.5, 1.3)	0.5 (-0.4, 1.3)	0.3 (-0.5, 1)	499	0.2 (-0.6, 1)	500	0.4 (-0.4, 1.1)	0.04	0.02	0.04
F∆HAZ	**Systolic BP**	504	0.3 (-1, 1.6)	0.3 (-1, 1.6)	0.1 (-1.1, 1.3)	499	0.1 (-1.2, 1.3)	500	0.3 (-0.9, 1.5)	0.02	0	0.02
F∆HAZ	**HAZ**	504	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	499	0.2 (0.1, 0.3)	500	0.2 (0.1, 0.3)	0.17	0.17	0.17
F∆HAZ	**WAZ**	503	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (0, 0.2)	498	0.1 (-0.1, 0.2)	499	0.1 (0, 0.2)	0.06	0.06	0.06
F∆HAZ	**BMI**	503	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	498	-0.1 (-0.2, 0)	499	-0.1 (-0.2, 0)	-0.08	-0.07	-0.06
F∆HAZ	**Knee-heel**	504	0.5 (0.3, 0.8)	0.5 (0.3, 0.8)	0.5 (0.2, 0.7)	499	0.5 (0.2, 0.7)	500	0.5 (0.2, 0.7)	0.19	0.17	0.16
F∆HAZ	**Head circ**	504	0 (-0.2, 0.1)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	499	0 (-0.2, 0.2)	500	0 (-0.2, 0.2)	-0.02	0	-0.01
F∆HAZ	**MUAC**	504	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	499	0 (-0.2, 0.2)	500	0 (-0.2, 0.2)	0.02	0.01	0.02
F∆HAZ	**Waist circ**	504	0.2 (-0.3, 0.7)	0.2 (-0.3, 0.7)	0.2 (-0.3, 0.7)	499	0.2 (-0.3, 0.7)	500	0.2 (-0.3, 0.7)	0.05	0.05	0.04
F∆HAZ	**Hip circ**	504	0.1 (-0.4, 0.7)	0.1 (-0.4, 0.7)	0 (-0.5, 0.6)	499	0 (-0.6, 0.6)	500	0.1 (-0.5, 0.6)	0.02	-0.01	0.01
F∆HAZ	**Calf circ**	504	0.1 (-0.1, 0.4)	0.1 (-0.1, 0.4)	0.1 (-0.1, 0.4)	499	0.1 (-0.2, 0.3)	500	0.1 (-0.1, 0.4)	0.05	0.03	0.05
F∆HAZ	**LMI**	499	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.1)	494	-0.1 (-0.2, 0.1)	495	0 (-0.2, 0.1)	0	-0.03	-0.02
F∆HAZ	**Imp Index**	499	0 (0, 0.1)	0 (0, 0.1)	0 (0, 0.1)	494	0 (0, 0.1)	495	0 (0, 0.1)	0.11	0.08	0.08
F∆HAZ	**Phase angle**	499	-0.1 (-0.1, 0)	-0.1 (-0.1, 0)	-0.1 (-0.1, 0)	494	-0.1 (-0.2, 0)	495	-0.1 (-0.1, 0)	-0.09	-0.09	-0.08
F∆HAZ	**Total SFT**	501	0.5 (-0.4, 1.3)	0.5 (-0.4, 1.3)	0.4 (-0.5, 1.2)	497	0.2 (-0.6, 1.1)	498	0.4 (-0.4, 1.2)	0.05	0.03	0.04
F∆HAZ	**Periphl SFT**	502	0.3 (-0.2, 0.8)	0.3 (-0.2, 0.8)	0.3 (-0.2, 0.8)	497	0.2 (-0.3, 0.7)	498	0.3 (-0.2, 0.8)	0.06	0.04	0.05
F∆HAZ	**Central SFT**	503	0.1 (-0.4, 0.5)	0.1 (-0.4, 0.5)	0.1 (-0.4, 0.5)	499	0 (-0.5, 0.5)	500	0.1 (-0.4, 0.5)	0.01	-0.01	0.01
F∆HAZ	**Hb**	504	0.1 (0, 0.2)	0.1 (0, 0.2)	0 (-0.1, 0.1)	499	0 (-0.1, 0.2)	500	0 (-0.1, 0.2)	0.03	0.02	0.02

Table A5-21 Associations of Catch-up in Height-for-age Z-score from 18 months to 7 years for girls (F HAZ Catch-up) with SAHARAN outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,. Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling.

Associations of catch-up in Height for age Z-score for Boys (M∆HAZ) from 18 months to 7 years and SAHARAN Outcomes

Boys' catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Model 3	n	Model 4 early	unadjusted	Adjusted m3 cont	Adjusted m4 early
M∆HAZ	MPI	477	1 (0, 2)	1 (0, 2)	1 (0, 2)	471	1 (0, 2)	471	1 (0, 2)	0.07	0.06	0.07
M∆HAZ	SAT	477	2 (-1, 4)	2 (-1, 4)	2 (-1, 4)	471	2 (-1, 4)	471	2 (0, 5)	0.05	0.05	0.05
M∆HAZ	Plus EF	472	0 (-2, 3)	0 (-2, 3)	0 (-2, 3)	466	1 (-2, 3)	466	0 (-2, 3)	0.01	0.02	0.01
M∆HAZ	Fine motor	474	-0.9 (-1.6, -0.3)	-0.8 (-1.5, -0.2)	-0.8 (-1.5, -0.2)	468	-0.8 (-1.5, -0.1)	468	-0.8 (-1.4, -0.1)	-0.1	-0.08	-0.08
M∆HAZ	SDQ	477	0 (0, 1)	0 (0, 1)	0 (0, 1)	471	0 (0, 1)	471	0 (0, 1)	0.06	0.05	0.04
M∆HAZ	Child Socioem	466	0 (0, 0)	0 (0, 0)	0 (0, 0)	471	0 (0, 0)	460	0 (0, 0)	0.03	0.02	0.04
M∆HAZ	Grip strength	477	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	471	0.2 (-0.1, 0.4)	471	0.2 (-0.1, 0.4)	0.07	0.06	0.06
M∆HAZ	Broad jump	475	2.4 (0.6, 4.2)	2.3 (0.5, 4.2)	2.3 (0.4, 4.2)	469	2.3 (0.3, 4.3)	469	1.9 (0, 3.9)	0.11	0.15	0.09
M∆HAZ	Shuttle run	476	-0.4 (-0.8, 0.1)	-0.4 (-0.8, 0.1)	-0.2 (-0.6, 0.2)	469	-0.2 (-0.6, 0.1)	469	-0.2 (-0.6, 0.2)	-0.09	-0.06	-0.06
M∆HAZ	Diastolic BP	475	0.5 (-0.3, 1.3)	0.5 (-0.3, 1.3)	0.4 (-0.4, 1.3)	469	0.4 (-0.5, 1.2)	469	0.6 (-0.3, 1.4)	0.05	0.03	0.06
M∆HAZ	Systolic BP	475	0.6 (-0.6, 1.8)	0.6 (-0.6, 1.8)	0.2 (-1, 1.3)	469	0.1 (-1, 1.3)	469	0.2 (-0.9, 1.4)	0.04	0.01	0.02
M∆HAZ	HAZ	477	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	471	0.2 (0.1, 0.3)	471	0.2 (0.1, 0.3)	0.15	0.16	0.16
M∆HAZ	WAZ	476	0.1 (0, 0.2)	0.1 (0, 0.2)	0.1 (0, 0.2)	470	0.1 (0, 0.2)	470	0.1 (0, 0.2)	0.08	0.08	0.08
M∆HAZ	BMI	476	0 (-0.1, 0)	0 (-0.1, 0)	0 (-0.1, 0.1)	470	-0.1 (-0.2, 0)	470	-0.1 (-0.2, 0.1)	-0.04	-0.05	-0.04
M∆HAZ	Knee-heel	476	0.3 (0.1, 0.6)	0.4 (0.1, 0.6)	0.3 (0, 0.6)	470	0.3 (0, 0.6)	470	0.3 (0, 0.6)	0.12	0.11	0.11
M∆HAZ	Head circ	477	0 (-0.2, 0.1)	0 (-0.2, 0.2)	0 (-0.1, 0.2)	470	0 (-0.1, 0.2)	470	0 (-0.1, 0.2)	-0.02	0.04	0.02
M∆HAZ	MUAC	476	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	470	0 (-0.1, 0.2)	470	0 (-0.1, 0.2)	0.03	0.03	0.02
M∆HAZ	Waist circ	476	0.2 (-0.2, 0.6)	0.2 (-0.2, 0.6)	0.2 (-0.2, 0.6)	470	0.1 (-0.2, 0.5)	470	0.1 (-0.3, 0.5)	0.04	0.03	0.03
M∆HAZ	Hip circ	477	0.6 (0.1, 1)	0.6 (0.1, 1.1)	0.5 (0.1, 1)	471	0.5 (0, 1)	471	0.5 (0, 1)	0.1	0.08	0.09
M∆HAZ	Calf circ	476	0.1 (-0.1, 0.4)	0.1 (-0.1, 0.4)	0.1 (-0.1, 0.3)	470	0.1 (-0.1, 0.3)	470	0.1 (-0.1, 0.3)	0.06	0.05	0.03
M∆HAZ	LMI	474	0 (-0.1, 0.2)	0 (-0.1, 0.2)	0.1 (-0.1, 0.2)	468	0.1 (-0.1, 0.2)	468	0 (-0.1, 0.2)	0.02	0.03	0.02
M∆HAZ	Imp Index	474	0 (0, 0.1)	0 (0, 0.1)	0 (0, 0.1)	468	0 (0, 0.1)	468	0 (0, 0.1)	0.12	0.11	0.1
M∆HAZ	Phase angle	474	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	468	0 (-0.1, 0.1)	468	0 (-0.1, 0.1)	0.01	0	0
M∆HAZ	Total SFT	477	0.2 (-0.5, 0.9)	0.3 (-0.4, 1)	0.1 (-0.6, 0.8)	471	0.1 (-0.6, 0.8)	471	0.1 (-0.6, 0.9)	0.03	0.01	0.01
M∆HAZ	Periphl SFT	477	0.1 (-0.4, 0.6)	0.1 (-0.3, 0.6)	0.1 (-0.4, 0.6)	471	0 (-0.4, 0.5)	471	0.1 (-0.4, 0.6)	0.02	0.01	0.01
M∆HAZ	Central SFT	477	0.1 (-0.2, 0.4)	0.1 (-0.2, 0.4)	0.1 (-0.2, 0.3)	471	0 (-0.2, 0.3)	471	0 (-0.2, 0.3)	0.03	0.01	0.01
M∆HAZ	Hb	477	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	471	0.1 (-0.1, 0.2)	471	0.1 (-0.1, 0.2)	0.04	0.04	0.05

Table A5-22 Associations of Catch-up in Height-for-age Z-score from 18 months to 7 years for boys (M HAZ Catch-up) with SAHARAN outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,.

Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling.

Associations of catch-up in Weight for age Z-score for Girls (F∆WAZ) from 18 months to 7 years and SAHARAN Outcomes

Catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Model 3 (cont)	n	Model 4(early)	unadjusted	Adjusted m3 cont	Adjusted m4 early
F∆WAZ	MPI	503	0 (-2, 1)	0 (-2, 1)	0 (-2, 1)	498	0 (-2, 1)	499	0 (-2, 1)	-0.02	-0.02	-0.01
F∆WAZ	SAT	503	1 (-2, 5)	2 (-2, 5)	1 (-2, 5)	498	1 (-2, 4)	499	2 (-2, 5)	0.04	0.02	0.04
F∆WAZ	Plus EF	496	2 (-1, 5)	2 (-1, 6)	2 (-1, 6)	491	2 (-1, 5)	492	2 (-1, 6)	0.06	0.07	0.08
F∆WAZ	Fine motor	502	-0.6 (-1.5, 0.3)	-0.6 (-1.5, 0.3)	-0.8 (-1.7, 0.2)	497	-0.7 (-1.6, 0.2)	498	-0.8 (-1.9, 0.2)	-0.07	-0.08	-0.1
F∆WAZ	SDQ	502	0 (0, 1)	0 (0, 1)	0 (0, 1)	498	0 (0, 1)	498	0 (0, 1)	0.01	0.03	0.02
F∆WAZ	Child Socioem	497	0 (0, 0)	0 (0, 0)	0 (0, 0)	492	0 (0, 0)	493	0 (0, 0)	0.01	0.01	0.02
F∆WAZ	Grip strength	503	0.3 (0, 0.5)	0.3 (0, 0.5)	0.3 (0, 0.5)	498	0.3 (0, 0.5)	499	0.3 (0, 0.6)	0.1	0.11	0.12
F∆WAZ	Broad jump	502	1.2 (-0.7, 3.2)	1.3 (-0.7, 3.2)	1.4 (-0.5, 3.2)	497	1.2 (-0.6, 3)	498	1.4 (-0.4, 3.2)	0.06	-0.07	0.07
F∆WAZ	Shuttle run	501	-0.1 (-0.4, 0.2)	-0.1 (-0.3, 0.2)	0 (-0.3, 0.3)	496	0 (-0.3, 0.2)	497	0 (-0.3, 0.3)	-0.02	-0.01	0
F∆WAZ	Diastolic BP	503	0.7 (0, 1.4)	0.7 (0.1, 1.4)	0.4 (-0.3, 1)	498	0.4 (-0.3, 1.1)	499	0.3 (-0.3, 0.9)	0.07	0.04	0.03
F∆WAZ	Systolic BP	503	0.5 (-0.5, 1.5)	0.5 (-0.5, 1.5)	0.1 (-0.9, 1.1)	498	0.1 (-0.9, 1.2)	499	0.1 (-1, 1.1)	0.04	0.01	0.01
F∆WAZ	HAZ	503	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	498	0.2 (0.1, 0.3)	499	0.2 (0.1, 0.3)	0.15	0.16	0.17
F∆WAZ	WAZ	503	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	498	0.3 (0.2, 0.4)	499	0.3 (0.2, 0.4)	0.28	0.27	0.28
F∆WAZ	BMI	503	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	498	0.3 (0.2, 0.4)	499	0.3 (0.2, 0.4)	0.27	0.26	0.26
F∆WAZ	Knee-heel	503	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.4 (0.1, 0.6)	498	0.4 (0.1, 0.6)	499	0.4 (0.1, 0.7)	0.17	0.16	0.16
F∆WAZ	Head circ	503	0 (-0.2, 0.1)	0 (-0.2, 0.1)	0 (-0.2, 0.1)	498	0 (-0.2, 0.1)	499	0 (-0.2, 0.2)	-0.02	-0.01	-0.01
F∆WAZ	MUAC	503	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.4 (0.2, 0.6)	498	0.4 (0.2, 0.6)	499	0.4 (0.2, 0.6)	0.25	0.24	0.24
F∆WAZ	Waist circ	503	0.9 (0.5, 1.3)	0.9 (0.5, 1.3)	0.9 (0.5, 1.2)	498	0.9 (0.5, 1.3)	499	0.9 (0.5, 1.3)	0.23	0.22	0.22
F∆WAZ	Hip circ	503	1.2 (0.7, 1.8)	1.2 (0.7, 1.8)	1.1 (0.6, 1.7)	498	1.1 (0.6, 1.7)	499	1.2 (0.6, 1.8)	0.24	0.22	0.23
F∆WAZ	Calf circ	503	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.4 (0.2, 0.7)	498	0.5 (0.2, 0.7)	499	0.5 (0.2, 0.7)	0.22	0.21	0.22
F∆WAZ	LMI	498	0.2 (0, 0.3)	0.2 (0, 0.3)	0.2 (0, 0.3)	493	0.2 (0, 0.3)	494	0.2 (0, 0.3)	0.09	0.1	0.11
F∆WAZ	Imp Index	498	0.1 (0, 0.1)	0.1 (0, 0.1)	0.1 (0, 0.1)	493	0.1 (0, 0.1)	494	0.1 (0, 0.1)	0.16	0.16	0.17
F∆WAZ	Phase angle	498	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0, 0.2)	493	0.1 (0, 0.2)	494	0.1 (0.1, 0.2)	0.18	0.15	0.17
F∆WAZ	Total SFT	500	1.8 (0.8, 2.8)	1.8 (0.8, 2.8)	1.7 (0.8, 2.7)	496	1.8 (0.9, 2.7)	497	1.8 (0.8, 2.8)	0.23	0.22	0.23
F∆WAZ	Periphl SFT	501	0.8 (0.3, 1.4)	0.9 (0.3, 1.4)	0.9 (0.3, 1.4)	496	0.9 (0.4, 1.4)	497	0.9 (0.3, 1.4)	0.17	0.18	0.19
F∆WAZ	Central SFT	502	1 (0.5, 1.4)	1 (0.5, 1.4)	0.9 (0.4, 1.3)	498	0.9 (0.4, 1.3)	499	0.9 (0.4, 1.4)	0.24	0.22	0.22
F∆WAZ	Hb	503	0 (-0.2, 0.1)	0 (-0.2, 0.1)	0 (-0.2, 0.1)	498	0 (-0.2, 0.1)	499	0 (-0.2, 0.1)	-0.01	-0.02	-0.02

Table A5-23 Associations of Catch-up in Weight-for-age Z-score from 18 months to 7 years for girls (F WAZ Catch-up) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,.

Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling.

Associations of catch-up in Weight for age Z-score for Boys (M∆WAZ) between 18 months to 7 years and SAHARAN Outcomes

Catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Adjusted difference Model 3 (	n	Model 4 early	unadjusted	Adjusted m3 cont	Adjusted m4 early
M∆WAZ	MPI	476	1 (0, 2)	1 (-1, 2)	1 (-1, 2)	470	1 (-1, 2)	470	1 (-1, 2)	0.05	0.04	0.04
M∆WAZ	SAT	476	1 (-2, 4)	0 (-3, 4)	0 (-3, 3)	470	0 (-2, 3)	470	0 (-3, 3)	0.01	0	0
M∆WAZ	Plus EF	471	0 (-2, 3)	0 (-2, 3)	0 (-2, 2)	465	0 (-2, 2)	465	0 (-3, 2)	0.01	0	-0.01
M∆WAZ	Fine motor	473	-0.6 (-1.2, 0)	-0.5 (-1.2, 0.1)	-0.4 (-1, 0.2)	467	-0.4 (-1, 0.2)	467	-0.4 (-1, 0.2)	-0.07	-0.04	-0.04
M∆WAZ	SDQ	476	0 (0, 1)	0 (0, 1)	0 (0, 1)	470	0 (0, 1)	470	0 (0, 1)	0.07	0.07	0.05
M∆WAZ	Child Socioem	465	0 (0, 0)	0 (0, 0)	0 (0, 0)	459	0 (0, 0)	459	0 (0, 0)	0.05	0.05	0.06
M∆WAZ	Grip strength	476	0.2 (0, 0.5)	0.2 (0, 0.5)	0.2 (0, 0.4)	470	0.2 (0, 0.4)	470	0.2 (0, 0.4)	0.1	0.09	0.08
M∆WAZ	Broad jump	474	1.9 (0.6, 3.2)	1.8 (0.5, 3.1)	1.9 (0.5, 3.2)	468	2.1 (0.6, 3.5)	468	1.8 (0.4, 3.1)	0.09	0.15	0.09
M∆WAZ	Shuttle run	475	0 (-0.3, 0.4)	0 (-0.4, 0.4)	0.1 (-0.3, 0.4)	468	0.1 (-0.2, 0.4)	468	0.1 (-0.2, 0.4)	0.01	0.03	0.03
M∆WAZ	Diastolic BP	474	-0.1 (-1, 0.9)	0 (-1, 0.9)	0 (-0.9, 0.9)	468	-0.1 (-1, 0.9)	468	0 (-0.9, 0.9)	-0.01	-0.01	0
M∆WAZ	Systolic BP	474	0.2 (-0.8, 1.2)	0.3 (-0.8, 1.3)	0.2 (-0.9, 1.2)	468	0.2 (-0.9, 1.3)	468	0.2 (-0.9, 1.2)	0.02	0.02	0.02
M∆WAZ	HAZ	476	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	470	0.2 (0.1, 0.3)	470	0.2 (0.1, 0.3)	0.17	0.18	0.17
M∆WAZ	WAZ	476	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	470	0.3 (0.2, 0.5)	470	0.3 (0.2, 0.5)	0.3	0.3	0.3
M∆WAZ	BMI	476	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	470	0.3 (0.2, 0.4)	470	0.3 (0.2, 0.4)	0.28	0.27	0.27
M∆WAZ	Knee-heel	475	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	469	0.4 (0.2, 0.7)	469	0.4 (0.1, 0.6)	0.17	0.16	0.15
M∆WAZ	Head circ	476	0 (-0.2, 0.1)	0 (-0.1, 0.2)	0 (-0.1, 0.2)	470	0.1 (-0.1, 0.2)	470	0.1 (-0.1, 0.2)	-0.01	0.04	0.03
M∆WAZ	MUAC	475	0.2 (0, 0.4)	0.2 (0, 0.3)	0.2 (0, 0.3)	469	0.2 (0, 0.3)	469	0.2 (0, 0.3)	0.12	0.11	0.1
M∆WAZ	Waist circ	475	0.8 (0.4, 1.1)	0.8 (0.4, 1.1)	0.8 (0.4, 1.1)	469	0.7 (0.4, 1.1)	469	0.7 (0.4, 1.1)	0.19	0.18	0.18
M∆WAZ	Hip circ	476	0.8 (0.3, 1.3)	0.8 (0.3, 1.3)	0.8 (0.3, 1.3)	470	0.7 (0.3, 1.2)	470	0.7 (0.3, 1.2)	0.16	0.14	0.14
M∆WAZ	Calf circ	475	0.4 (0.1, 0.6)	0.4 (0.1, 0.6)	0.4 (0.1, 0.6)	469	0.3 (0.1, 0.5)	469	0.3 (0.1, 0.5)	0.17	0.15	0.15
M∆WAZ	LMI	473	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	467	0.2 (0.1, 0.4)	467	0.2 (0.1, 0.4)	0.13	0.14	0.13
M∆WAZ	Imp Index	473	0.1 (0, 0.1)	0.1 (0, 0.1)	0.1 (0, 0.1)	467	0.1 (0, 0.1)	467	0.1 (0, 0.1)	0.2	0.21	0.2
M∆WAZ	Phase angle	473	0.1 (0, 0.1)	0.1 (0, 0.1)	0.1 (0, 0.1)	467	0.1 (0, 0.1)	467	0.1 (0, 0.1)	0.12	0.11	0.11
M∆WAZ	Total SFT	476	0.5 (-0.2, 1.1)	0.4 (-0.2, 1.1)	0.4 (-0.2, 1.1)	470	0.3 (-0.2, 0.9)	470	0.4 (-0.2, 1.1)	0.06	0.04	0.05
M∆WAZ	Periphl SFT	476	0.2 (-0.3, 0.6)	0.2 (-0.3, 0.6)	0.2 (-0.3, 0.6)	470	0.1 (-0.3, 0.5)	470	0.2 (-0.3, 0.6)	0.03	0.02	0.03
M∆WAZ	Central SFT	476	0.3 (0, 0.6)	0.3 (0, 0.6)	0.3 (0, 0.5)	470	0.2 (0, 0.5)	470	0.3 (0, 0.5)	0.07	0.06	0.07

Catch-up in Height Z-score from 18mo to 7yr	School-age Outcomes	GEE Mean difference (95% CI)								Standardised		
		n	Unadjusted	Model 1	Model 2	n	Adjusted difference Model 3 (	n	Model 4 early	unadjusted	Adjusted m3 cont	Adjusted m4 early
M∆WAZ	Hb	476	0 (-0.2, 0.1)	0 (-0.2, 0.1)	0 (-0.2, 0.1)	470	0 (-0.2, 0.1)	470	0 (-0.2, 0.1)	-0.02	-0.03	-0.01

Table A5-24 Associations of Catch-up in Weight-for-age Z-score from 18 months to 7 years for girls (M WAZ Catch-up) with SAHARAN toolbox outcomes.

From top: MPI: Mental processing index (KABC-II total), SAT: School achievement test, PlusEF: Executive function total, Fine motor: coordination from finger tapping test (seconds), SDQ: Strength and difficulties questionnaire total (Socioemotional function), Child Socioem: Child's own socioemotional score, Grip strength: Handgrip strength (Kg),Broad Jump: broad jump distance (cm), Shuttle Run: Cardiovascular fitness (VO_2max from shuttle run test), Diastolic BP: Diastolic Blood pressure, Systolic BP: Systolic blood pressure, HAZ: Height-for-age Z-score at 7 years, WAZ: Weight-for-age Z-score at 7 years, BMI: BMI-for-age Z-score at 7 years., Knee-heelH: Knee-heel length (cm), Head circ: head circumference (cm), MUAC: Mid-upper arm circumference (cm), Waist circ: waist circumference (cm), Hip circ: hip circumference (cm), calf circ: calf circumference (cm), LMI: Bioimpedance lean mass index Kg/m^2, Imp Index: Impedance index m^2 $Ohms^{-1}$, Phase angle: Bioimpedance phase angle (degrees), Total SFT: Total skinfold thickness (mm), Periphl SFT: peripheral skinfold thickness (mm), Central SFT: Central Skinfold thickness (mm), Hb: Haemoglobin, g dl^{-1}, Model 1: SHINE trial arm,. Model 2:Trial factors : SHINE trial arm, sex, DC, calendar age recruited, temperature, age of child, Model 3: Trial factors plus child years and months of schooling, discipline score, caregiver Edinburgh Postnatal Depression Score (EPDS), Household Food Insecurity Assessment Scale total (HFIAS), household religion, household socioeconomic status (SES), Caregiver social support score, household adversity score, number of children's books, caregiver years of schooling and caregiver gender norms score. Model 4: Trial factors plus breastfeeding duration, birthweight, baseline maternal depression score (EPDS), household dietary score, maternal haemoglobin, baseline socioeconomic status, born in facility, maternal height and maternal schooling

A5-9 Differences in baseline environmental variables by child sex

Baseline Variables	female N1	Mean (SD)	Male N2	Mean (SD)	p-value:
Duration breastfed, months	479	19 (4)	463	19 (4)	0.65
Household size	483	5 (2)	472	5 (2)	0.36
Socioeconomic score	469	0.2 (1.8)	448	0.1 (1.8)	0.26
Coping Strategies Index (CSI)	459	5 (11)	439	4 (8)	0.25
Mother age, year	446	25 (6)	440	26 (6)	0.02
Mother height, cm	491	159.8 (6)	472	160 (5.9)	0.64
Mother MUAC, cm	502	26.7 (3.4)	477	26.5 (3)	0.47
Mother Hb, g/dl	415	12.2 (1.4)	395	12.2 (1.4)	1.00
Mother schooling, years	477	10 (2)	468	10 (2)	0.13
Parity	363	2 (1)	347	2 (1)	0.26
Maternal Gender norms score	470	2 (1)	445	2 (1)	0.32
Maternal social support score	456	4 (1)	441	4 (1)	0.39

Table A5-25 Comparison of baseline environmental and maternal variables by child sex,

Coping Strategies Index is a measure of food insecurity, where higher scores have greater food insecurity, socioeconomic score is from a wealth index derived previously[139]. Gender norms is a measure of maternal attitudes to gender relations, including attitudes to schooling for girls, with more positive values associated with more progressive values[140]. Social support is a measure of the mother's opinion for sources of community support for advice and access to help on problems, with higher scores indicating more support[140].

9.4 Chapter 6 Appendix

A6-1 Directed Acyclic Graph for Contemporary Covariates

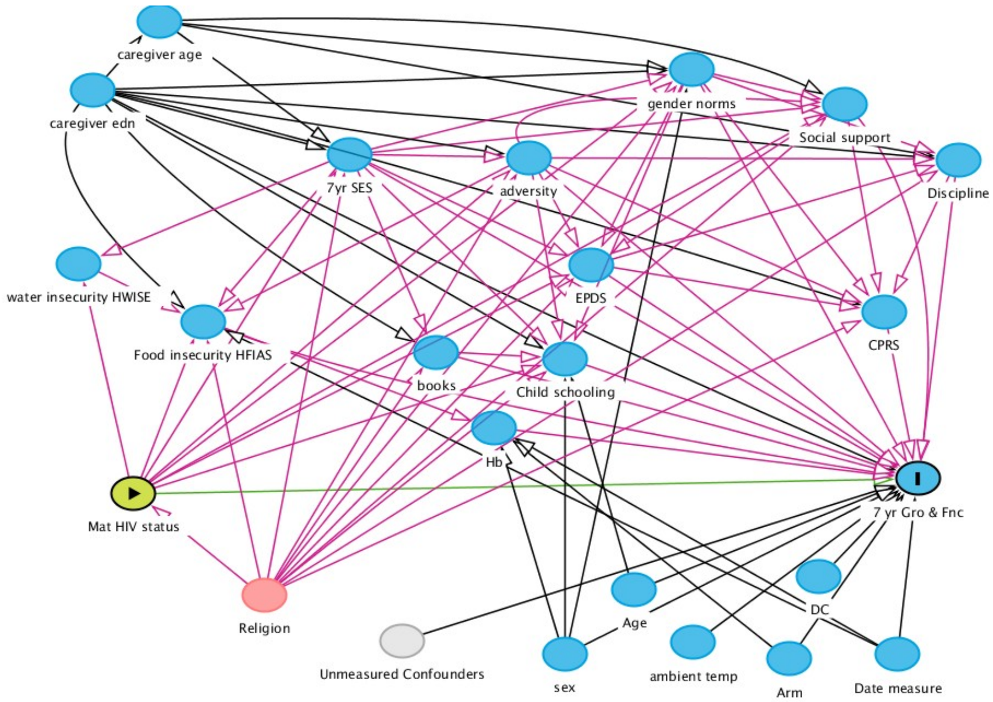


Figure A6-1: : DAG used to determine covariates for Model 2 (contemporary)

The directed acyclic graphs was used to identify the confounding variables that were required within adjusted models for the effect of maternal HIV on school-age outcomes for contemporary covariates. Hence the DAG was drawn on Dagitty and the variables for adjustment were identified before examining the data in detail. Adjustment was performed for contemporary covariates asked in the contemporary questionnaire. DC: Data collector, sex: Child sex, Arm: SHINE trial intervention arm, Date measure: calendar quarter when measurement performed, Exact age: exact age of child, ambient temperature: average temperature during SAHARAN toolbox measurements, Confounders: unmeasured confounders, Caregiver edn: Caregiver schooling in number of years, Caregiver age: age of primary caregiver at 7 year visit, 7yr SES: contemporary socioeconomic status (wealth index), adversity: contemporary adversity score,, EPDS: contemporary caregiver Edinburgh Postnatal Depression Score, Gender norms: contemporary caregiver gender norm scale, Social support: contemporary caregiver social support scale, Water insecurity (HWISE): Household water insecurity experiences scale, Food insecurity (HFIAS): Household food insecurity experiences scale, Books: number of children's books at home, Child schooling: Total child schooling in years and months, Hb: child contemporary haemoglobin measured during visit, CPRS: Child parent relationship scale (measure of nurturing), Discipline: child discipline scale, Religion: household religion, mat HIV: Maternal HIV status during pregnancy (the exposure), 7yr Gro & fnc: child growth, cognitive and physical function at 7 years (the outcome). Adjustment variables for model 2 were arm, DC, age of child, calendar age recruited, temperature, sex, Socioeconomic status, Caregiver depression measure (EPDS), Household food insecurity (HFIAS), Household religion, Caregiver social support, Caregiver gender norms, Caregiver age, Caregiver education, Adversity score, Children's books at home.

A6-2 Directed Acyclic Graph for Baseline Factors

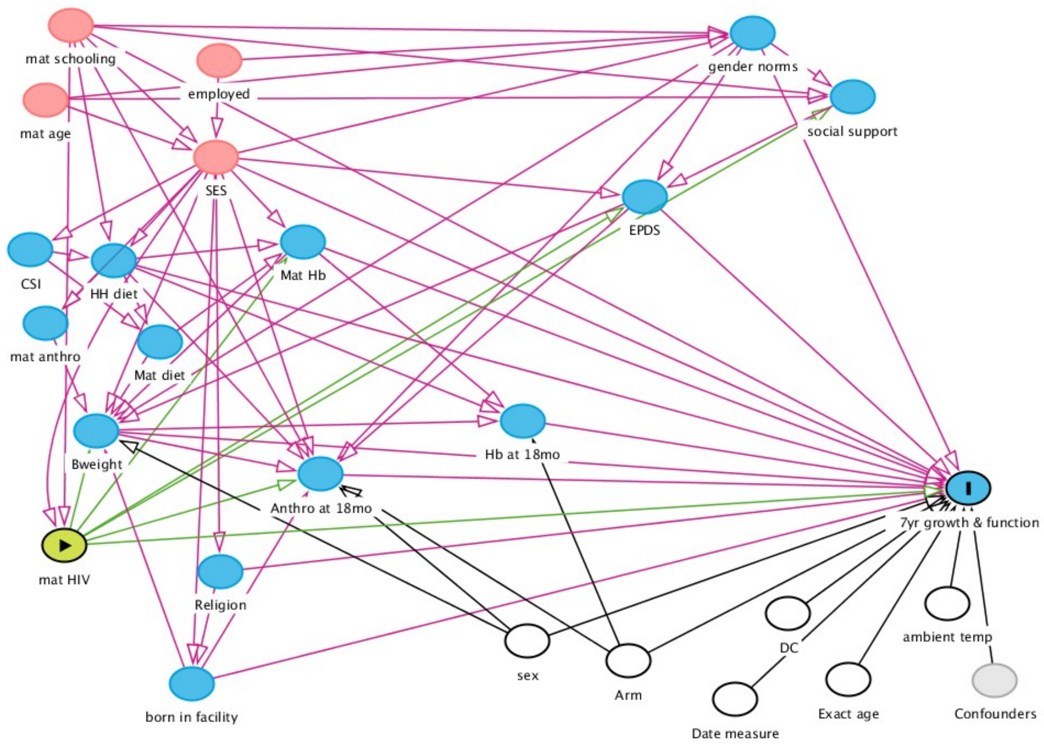


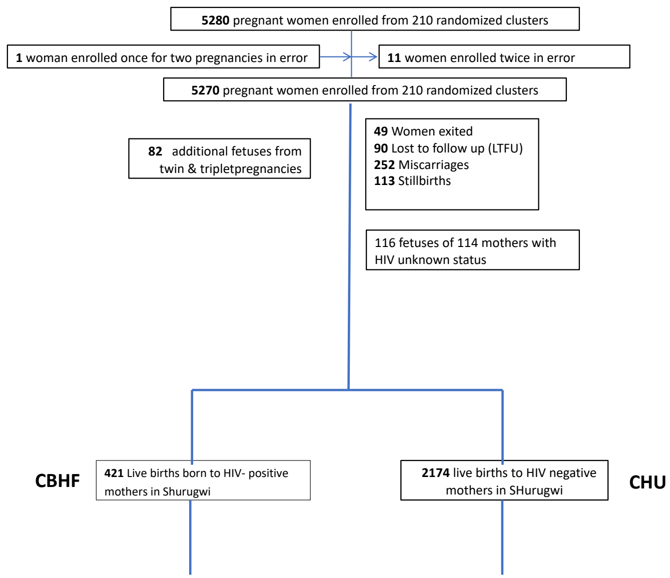
Figure A6-2: DAG used to determine covariates for Model 3 (baseline)

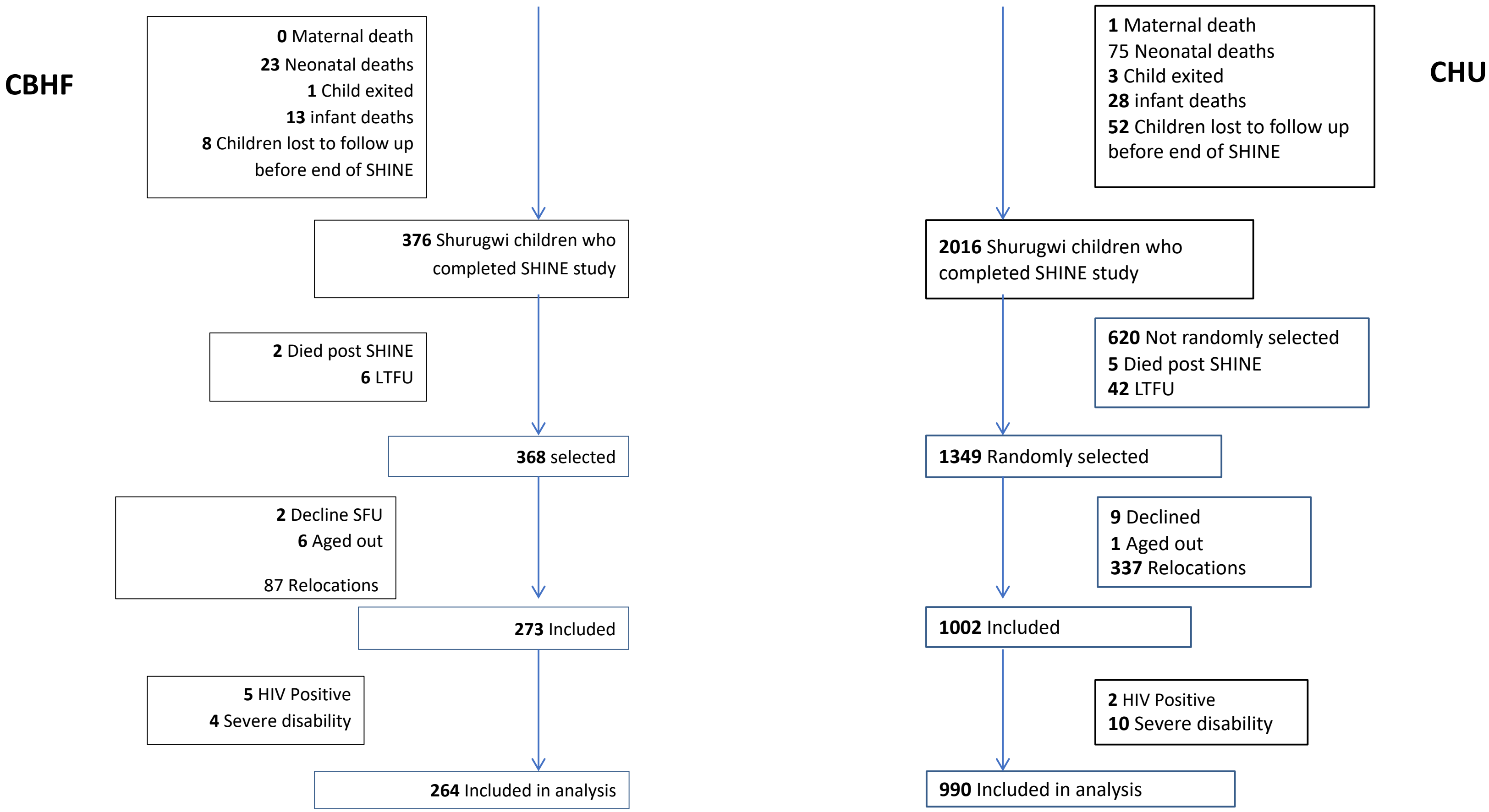
The directed acyclic graphs was used to identify the confounding variables that were required within adjusted models for the effect of maternal HIV on school-age outcomes for baseline covariates. Hence the DAG was drawn on Dagitty and the variables for adjustment were identified before examining the data in detail. Adjustment was performed for early-life covariates asked in the baseline questionnaire and early-life child measurements. DC: Data collector, sex: Child sex, Arm: SHINE trial intervention arm, Date measure :calendar quarter when measurement performed, Exact age: exact age of child, ambient temperature: average temperature during SAHARAN toolbox measurements, Confounders: unmeasured confounders, Mat schooling: Maternal schooling in number of years, mat age: maternal age, SES: baseline socioeconomic status (wealth index), employed: whether mother was employed or not, EPDS: Baseline maternal Edinburgh postnatal depression score, Gender norms: baseline maternal gender norm scale, social support: baseline maternal social support scale, CSI: Coping strategies index (measure of food insecurity), HH diet: household dietary score, Mat HB: Maternal haemoglobin in pregnancy, Mat diet: maternal diet score, Mat anthro: Maternal anthropometry (note height was used in model), Bweight: child birthweight, mat HIV: Maternal HIV status during pregnancy (the exposure), anthro at 18 months: child anthropometry at 18 months (length-for-age-z-score used in model), religion: household religion, Hb at 18 months: child haemoglobin at 18 months of age. Adjustment variables were: Arm, cata collector, age of child, calendar age recruited, temperature, Anthropometry at 18mo, Birthweight, maternal depression score (EPDS), household dietary score, maternal haemoglobin in pregnancy, baseline socioeconomic scale, born in facility, gender norms, maternal years of schooling.

A6-3 CONSORT diagram for CBHF and CHU

Figure A6-3 CONSORT diagram showing CBHF and CHU selected into SHINE Follow-up.

For the CONSORT diagram of CBHF and CHU, 6 children born to mothers living with HIV (MLWH) aged out because initially children with known HIV positive status were not included for measurement. 1 child born to HIV negative mothers also aged out due to heavy rains making their area inaccessible before they turned 8 years. Participants were recorded as lost to follow-up (LTFU) at three stages: shortly after enrolment into the study during pregnancy, during the first 18 months before the trial primary endpoint was measured, or between 18 months and 7 years when they were unable to be located. Children with severe disability or who were HIV positive were not included in this analysis.




CBHF
0 Maternal death
23 Neonatal deaths
1 Child exited
13 infant deaths
8 Children lost to follow up before end of SHINE
376 Shurugwi children who completed SHINE study
2 Died post SHINE
6 LTFU
368 selected
2 Decline SFU
6 Aged out
87 Relocations
273 Included
5 HIV Positive
4 Severe disability
264 Included in analysis
CHU
1 Maternal death
75 Neonatal deaths
3 Child exited
28 infant deaths
52 Children lost to follow up before end of SHINE
2016 Shurugwi children who completed SHINE study
620 Not randomly selected
5 Died post SHINE
42 LTFU
1349 Randomly selected
9 Declined
1 Aged out
337 Relocations
1002 Included
2 HIV Positive
10 Severe disability
990 Included in analysis

A6-4 Adversity scores within CBHF

Adversity for children born to mothers without HIV	Number of households
Death in household	37% [97]
2 or more deaths in household	8% [20]
Household member lost paid employment	14% [36]
Household member unemployed >6 months	12% [30]
Household had crop failure	48% [124]
Household had 2 or more crop failures	35% [77]
Household had business failure	31% [79]
Household lost land	3% [8]
Household lost family possessions	16% [41]
Adults in household that are sick or injured, so not able to work for >3 months	13% [34]
Household member with alcohol problem	6% [15]
Household debt causes worry	16% [42]
Have move home 3 or more times since child in SHINE study born	4% [10]
Caregiver was sad or very sad about the last household move	11% [25]
Child in SHINE admitted to hospital overnight	10% [27]
Child in SHINE study had 2 or more hospital admissions	2% [4]
Caregiver separated from child for more than 3 months more than once	4% [11]
Households with no documented adversity	17% [44]

Table A6-1 Adversities for children born from mothers living with HIV

A6-4 Definition of disability for CBHF

CBHF	WG UNICEF scoring					
Child number	Functional difficulty	Severe Functional difficulty	Learning difficulty	Severe learning difficulty	Definition	Further explanation from Data Collector notes
C11	0	1	0	1	Cognitive disability	Down Syndrome
C12	1	0	0	1	Cognitive disability	Delayed milestones and not able to perform tasks
C13	0	0	0	0	Cognitive disability	Difficulty moving hands and understanding tasks
C14	0	0	0	0	Cognitive disability	Paralysed on RHS, poor concentration & engagement
SRT4	1	1	0	0	Shuttle run disability	Lower limb disability
SRT5, BJ2	0	0	0	0	Shuttle run & broadjump disability	Injured leg pricked by nail
SRT6, BJ3	0	0	0	0	Shuttle run & broadjump disability	Child limping
SRT7, GS1, BJ4,	1	0	1	0	Shuttle run, grip strength & broadjump disability	Child not engaged in physical tasks but did cognitive tasks
SRT8, BJ5	0	0	0	0	Shuttle run & broadjump disability	Asthmatic child

Table A6-2 Definitions of disability for CBHF

Disability was defined using both WG UNICEF screening tool and clinical comments by the data collector for CBHF

A6-5 Baseline comparisons of CBHF and CHU

Table A6-3 Baseline comparison of SFU enrolment and those not enrolled for children from MLWH

Comparison of household, environmental and child characteristics between those enrolled into SHINE follow-up and those not enrolled, for children born from mothers living with HIV (MLWH)

Domain	Baseline variables for Women living with HIV and their children born	Included in SHINE follow-up	Not included in SHINE follow-up	p-value
Participant numbers	Caregiver assessed, N*	267	459	
	Children assessed, N	273	465	
Household	Median number of occupants [IQR]	4.0 (3.0 ; 6.0)	4.0 (3.0 ; 6.0)	0.03
	Wealth quintile, n (%)			
Wealth Quintile	Lowest	64/258 (24.8%)	129/453 (28.5%)	0.49
	Second	55/258 (21.3%)	108/453 (23.8%)	
	Middle	57/258 (22.1%)	83/453 (18.3%)	
	Fourth	41/258 (15.9%)	63/453 (13.9%)	
	Highest	41/258 (15.9%)	70/453 (15.5%)	
Electricity	Electricity in home, n (%)	6/260 (2.3%)	13/452 (2.9%)	0.65
	Other electric power, n (%)			
	Generator	9/260 (3.5%)	9/453 (2.0%)	0.10
	Solar panel	171/260 (65.8%)	269/453 (59.4%)	
	Inverter	5/260 (1.9%)	8/453 (1.8%)	
	No other type	75/260 (28.9%)	167/453 (36.9%)	
Sanitation	Any latrine at household, n (%)	92/255 (36.1%)	142/447 (31.8%)	0.28
	Improved latrine at household, n (%)	79/255 (31.0%)	124/446 (27.8%)	0.42
Water	Main source of household drinking water improved, n (%)	159/255 (62.4%)	263/446 (59.0%)	0.46
	Treat drinking water to make it safer, n (%)	28/255 (11.0%)	56/438 (12.8%)	0.50

Domain	Baseline variables for Women living with HIV and their children born	Included in SHINE follow-up	Not included in SHINE follow-up	p-value
	One-way walk time to fetch drinking water (min) , median (IQR)	10.0 (5.0 ; 25.0)	10.0 (5.0 ; 20.0)	0.01
	Per capita water volume collected past 24 hr, median (IQR)	6.7 (4.0 ; 10.0)	8.6 (5.0 ; 13.3)	<0.001
Hygiene	Handwashing station at household, n (%)	35/246 (14.2%)	33/412 (8.0%)	0.02
	Improved floor, n (%)	115/258 (44.6%)	222/444 (50.0%)	0.20
	Number of chickens, median (IQR)	5.0 (2.0 ; 10.0)	4.0 (0.0 ; 8.0)	0.01
	Livestock observed inside the house, n (%)	103/258 (39.9%)	140/453 (30.0%)	0.02
	Faeces observed in the yard, n (%)	86/256 (33.6%)	123/450 (27.3%)	0.09
Diet and food security	Household meets minimum dietary diversity score, n (%)	85/243 (35.0%)	151/369 (40.9%)	0.15
	Coping strategies index, median (IQR)	3.0 (0.0 ; 9.0)	2.0 (0.0 ; 12.0)	0.12
Maternal Characteristics	Mean age (SD), years	30.2 (6.1)	28.6 (6.3)	<0.001
	Mean height (SD), cm	160.2 (6.2)	160.2 (6.2)	0.88
	Mean mid-upper-arm circumference (SD), cm	26.5 (2.8)	26.1 (3.00	0.01
	Mean maternal Hb (SD), g/dL	11.5 (1.4)	11.1 (1.8)	0.01
	Mother meets minimum dietary diversity score, n (%)	90/250 (36.0%)	182/439 (41.5%)	0.16
	Mean years of schooling completed (SD)	9.2 (1.9)	9.1 (2.2)	0.54
	Median parity (IQR)	2.0 (1.0 ; 3.0)	2.0 (1.0 ; 3.0)	0.01
	Married, n (%)	231/248 (93.2%)	412/434 (94.9%)	0.71
	Employed, n (%)	17/260 (6.5%)	50/450 (11.1%)	0.04
	Religion, n (%)			
	Apostolic	118/252 (46.8%)	212/437 (48.5%)	0.85
	Other Christian	106/252 (42.1%)	182/437 (41.7%)	
	Other religion	28/252 (11.1%)	43/437 (9.8%)	
	Median Gender norms attitudes (IQR)	1.8 (1.5 ; 3.0)	1.7 (1.5 ; 3.0)	0.57
	Median Perceived social support (IQR)	3.5 (3.0 ; 3.9)	3.5 (3.1 ; 4.0)	0.04
	Median EPDS depression scale (IQR)	2.0 (0.0 ; 8.0)	2.0 (0.0 ; 6.0)	0.01
Infant characteristics	Female, n (%)	137/273 (50.2%)	230/460 (50.0%)	0.96
	Mean birth weight (SD), kg	3.0 (0.5)	3.0 (0.5)	0.01
	Low birthweight, n (%)	26/254 (10.2%)	58/397 (14.6%)	0.10
	Institutional delivery, n (%)	216/247 (87.5%)	328/402 (81.6%)	0.06

Domain	Baseline variables for Women living with HIV and their children born	Included in SHINE follow-up	Not included in SHINE follow-up	p-value
	Vaginal delivery, n (%)	240/258 (93.0%)	369/401 (92.0%)	0.73
18-month characteristics	Mean LAZ at 18 months, (SD)	-1.9 (1.1)	-1.9 (1.2)	0.92
	Mean WAZ at 18 months, (SD)	-1.0 (1.1)	-0.9 (1.1)	0.51
	Mean WHZ at 18 months, (SD)	-0.1 (1.1)	-0.02 (1.2)	0.31
	Mean Head circumference Z score at 18 months, (SD)	-0.5 (1.1)	-0.5 (1.2)	0.90
	Mean MUAC Z score at 18 months, cm (SD)	-0.1 (0.9)	-0.2 (0.9)	0.01
	Mean Hb at 18 months, g/dL (SD)	11.8 (1.2)	11.8 (1.2)	0.79

Table A6-4 Comparison of baseline pregnancy and 18-month measurements for CBHF and CHU

Comparison of maternal, household, environmental and child characteristics between Children born HIV free (CBHF) from mothers living with HIV and children unexposed to HIV (CHU).

Domain	Baseline characteristics	CBHF	CHU	p-value
Pregnancy	Mean age (SD), years	30.3 (6.0)	25.7 (6.3)	<0.001
	Mean height (SD), cm	160.4 (6.1)	160.0 (6.0)	0.35
	Mean MUAC (SD), cm	26.6 (2.8)	26.6 (3.2)	0.99
	Mean haemoglobin (SD), g/dl	11.5 (1.4)	12.2 (1.4)	<0.001
	Mean years of schooling (SD)	9.1 (1.9)	9.7 (1.7)	<0.001
	Median parity (IQR)	2 (1, 3)	2 (1, 3)	<0.001
	Married, % [N]	93.5% [229/245]	95.2% [893/938]	0.45
	Employed, % [N]	6.6% [17/256]	7.5% [69/919]	0.64
Maternal religion	Apostolic, % [N]	45.6% [113]	48.1% [454]	0.60
	Other Christian	42.7% [106]	42.0% [398]	
	Other non-Christian	11.7% [29]	9.8% [92]	
Maternal capabilities	Mean Gender norms (SD)	2.2 (0.8)	2.3 (0.8)	0.16
	Mean perceived social support (SD)	3.4 (0.7)	3.5 (0.6)	0.03
	Mean Edinburgh Postnatal Depression Score (SD)	4.6 (5.6)	2.8 (4.0)	<0.001
Household	Median household size (IQR)	4 (3, 6)	5 (4, 6)	0.08
	Median Coping Strategies Index (IQR)	3 (0, 9)	0 (0, 9)	<0.001
Baseline wealth quintile	lowest	25.2% [64 /254]	17.7% [162 / 917]	0.007
	second	21.7% [55 / 254]	18.4% [169 / 917]	

Domain	Baseline characteristics	CBHF	CHU	p-value
	middle	21.7% [55 / 254]	20.5% [188 / 917]	
	fourth	15.0% [38 / 254]	21.7% [199 / 917]	
	highest	16.5% [42 / 254]	21.7% [199 / 917]	
Electricity	Electricity in house, % [N]	2.3% [6 / 256]	3.4% [31 / 917]	0.40
Sanitation	Any latrine, % [N]	36.3% [91 / 251]	38.0% [343 / 902]	0.61
	Improved latrine, % [N]	30.7% [77 / 251]	32.1% [289 / 901]	0.67
Water	Improved water source, % [N]	61.8% [155 / 251]	68.3% [617 / 903]	0.05
	Treat drinking water in any way, % [N]	11.2% [28 / 251]	14.5% [130 / 898]	0.18
Diet	HH meets minimum dietary diversity, % [N]	36.4% [87 / 239]	37.7% [333 / 884]	0.72
	Women meet minimum dietary diversity score, % [N]	37.4% [92 / 246]	36.8% [333/ 904]	0.87
Child	Mean Birthweight, Kg (SD)	3.03 (0.46)	3.10 (0.47)	0.06
	Proportion Low Birthweight, % [N]	10.2% [25 / 246]	9.2% s[87 / 945]	0.65
	Proportion Institutional delivery, % [N]	87.0% [207 / 238]	91.4% [844 / 923]	0.04
	Proportion vaginal delivery, % [N]	93.2% [232 / 249]	94.4% [900 / 953]	0.45
	Mean breastfeeding duration, months (SD)	17.7 (4.5)	19.1 (3.7)	<0.001
18 Month Child Outcomes	Mean 18-month LAZ (SD)	-1.83 (1.06)	-1.50 (1.02)	<0.001
	Stunted at 18 months, % [N]	45.2% [118 / 261]	29.6% [290 / 981]	<0.001
	Mean 18-month WAZ (SD)	-0.96 (1.05)	-0.74 (0.98)	0.003
	Underweight at 18 months, % [N]	16.9% [44 / 261]	8.8% [86 / 981]	<0.001
	Mean 18-month WHZ (SD)	-0.11 (1.06)	-0.03 (1.00)	0.28
	Mean 18-month HCZ (SD)	-0.46 (1.07)	-0.21 (0.98)	0.001

Domain	Baseline characteristics	CBHF	CHU	p-value
	Mean 18-month MUACZ (SD)	-0.06 (0.87)	0.10 (0.87)	0.01
	Mean 18-month Hb, g/dL (SD)	11.8 (1.1)	11.8 (1.1)	0.93

A6-6 Detailed secondary outcomes for CBHF and CHU

Table A6-5 Secondary cognitive outcomes comparing CBHF and CHU by subtest

Cognitive function included the Kaufman Assessment Battery for Children (KABC-II) with its 8 subtests Atlantis, Story completion, Number recall, Delayed Atlantis, Rover, Triangles, Word Order and Pattern reasoning. 2 from each of these 8 subtests were added together to form the 4 cognitive domains of Sequential (Number recall + word order), Planning (Story completion + pattern reasoning), Learning (Atlantis + Atlantis Delayed) and Simultaneous (Rover + Triangles) domains. The School Achievement Test (SAT) was formed of numeracy, reading and writing sections. The Plus-EF total was formed of 3 subtests Multi-Source Interference Test (MSIT), Stars and Flowers and Fish Flanker. The Fine motor (FM) test was measured by sequential finger tapping for both dominant and non-dominant hands, using seconds as a unit and hence a higher number represented slower fine motor coordination. The Strength and Difficulties Questionnaire (SDQ) total was measured using 4 subscales of emotional, conduct, hyperactivity and inattention with higher scores representing more difficulties. In addition the prosocial subscale was separately measured for positive behaviour. The child socioemotional sub-score was the total with one question removed on food security. Model 1 adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling).

Outcome		CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
Test	Cognitive subtests	N	Mean (SD)	N	Mean (SD)	Unadjusted	Adjusted difference Model 1 (Trial factors)	Adjusted difference Model 2 (Trial factors & contemporary covariates)	Adjusted difference Model 3 (Trial factors & baseline covariates)
KABC-II domain & subtest	Atlantis	264	6 (2)	990	6 (2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
	Story completion	264	4 (2)	990	5 (2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Number recall	264	7 (2)	990	7 (2)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 1)
	Atlantis delayed	264	7 (2)	990	7 (2)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 1)
	Rover	264	7 (2)	990	7 (2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
	Triangles	264	4 (2)	990	4 (2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
	Word Order	264	5 (2)	990	6 (2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)

Outcome		CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
	Pattern reasoning	264	5 (2)	990	6 (3)	1 (0, 1)	1 (0, 1)	0 (0, 1)	0 (0, 1)
	Learning (domain)	264	13 (3)	990	13 (4)	1 (0, 1)	1 (0, 1)	1 (0, 1)	1 (0, 1)
	Planning (domain)	264	10 (3)	990	11 (4)	1 (0, 1)	1 (0, 1)	0 (0, 1)	1 (0, 1)
	Simultaneous (domain)	264	10 (3)	990	11 (4)	1 (0, 1)	1 (0, 1)	1 (0, 1)	1 (0, 1)
	Sequential (domain)	264	12 (4)	990	13 (4)	1 (0, 1)	1 (0, 1)	1 (0, 1)	1 (0, 1)
SAT	Numeracy	264	17 (6)	990	18 (6)	2 (1, 2)	2 (1, 2)	1 (0, 2)	1 (0, 2)
	Reading	264	10 (12)	990	14 (13)	3 (2, 5)	3 (2, 5)	2 (1, 4)	3 (1, 5)
	Writing	264	12 (9)	990	14 (10)	2 (1, 3)	2 (1, 3)	2 (0, 3)	2 (1, 3)
Plus-EF	Multi-source interference test (MSIT)	251	22 (11)	978	24 (11)	2 (1, 4)	2 (1, 3)	2 (0, 3)	2 (0, 3)
	Stars and Flowers	251	41 (10)	978	43 (9)	2 (0, 3)	2 (0, 3)	1 (0, 3)	2 (0, 3)
	Fish flanker	251	46 (12)	978	47 (12)	1 (0, 3)	1 (0, 3)	1 (-1, 2)	1 (-1, 2)
FM	Finger tapping (dominant), sec	262	24 (7)	986	23 (7)	-1 (-1.8, -0.2)	-1.1 (-1.9, -0.2)	-0.5 (-1.3, 0.4)	-0.7 (-1.6, 0.1)
	Finger tapping (non-dominant), sec	262	26 (7)	986	25 (7)	-0.9 (-1.9, 0)	-1 (-2, 0)	-0.5 (-1.5, 0.5)	-0.7 (-1.7, 0.3)
SDQ	Emotional	263	2 (2)	989	2 (2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Conduct	263	2 (2)	989	2 (2)	0 (0, 0)	0 (-1, 0)	0 (0, 0)	0 (0, 0)
	Hyperactivity / attention	263	4 (2)	989	4 (2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Peer relationships	263	1 (1)	989	1 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Prosocial	263	8 (2)	989	8 (2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
CSE	Child socioemotional (removing food security)	256	4 (1)	973	4 (1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Table A6-6 Secondary physical outcomes comparing CBHF and CHU.

Outcome		CBHF		CHU		GEE Mean difference (95% CI) of CHU vs CBHF			
Test	**Physical function subtests**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Unadjusted**	**Adjusted difference Model 1 (Trial factors)**	**Adjusted difference Model 2 (Trial factors & contemporary covariates)**	**Adjusted difference Model 3 (Trial factors & baseline covariates)**
Grip	Grip strength dominant hand, Kg	262	10.6 (2.1)	990	10.8 (2.0)	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	0.2 (0, 0.5)	0.1 (-0.3, 0.4)
	Grip strength non-dominant hand, Kg	262	10.4 (1.9)	990	10.6 (2.1)	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.5)	0 (-0.3, 0.3)
	Standardised Grip strength (a)	262	-0.1 (1)	990	0.0 (1.0)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0, 0.2)	0 (-0.1, 0.2)
BJ	Standardised Broad jump (b)	259	-0.1 (1.1)	987	0.0 (1.0)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0, 0.2)	0.1 (-0.1, 0.2)
Run	**Standardised VO2max (c)***	**255**	**-0.2 (1)**	**986**	**0.1 (1.0)**	**0.3 (0.1, 0.4)**	**0.2 (0.1, 0.4)**	**0.2 (0, 0.3)**	**0.1 (0, 0.3)**
Tot	Physical function (a)+(b)+(c)	254	-0.3 (2)	984	0.1 (2.1)	0.4 (0.1, 0.7)	0.4 (0.1, 0.7)	0.3 (0.1, 0.6)	0.2 (-0.1, 0.4)
Blood pressure	Resting pulse pressure, mm Hg	264	34 (7)	988	35 (7)	1 (0, 2)	1 (0, 2)	1 (0, 1)	0 (0, 1)
	Systolic BP 1 min after SRT, mm Hg	256	125 (11)	976	127 (11)	1 (0, 3)	1 (0, 3)	1 (-1, 2)	1 (-1, 2)
	Diastolic BP 1 min after SRT, mm Hg	256	85 (12)	985	86 (11)	1 (-1, 3)	1 (-1, 3)	1 (-1, 2)	1 (-1, 2)
	Pulse pressure 1 min after SRT, mm HG	256	39 (9)	985	40 (9)	1 (0, 2)	1 (0, 2)	0 (-1, 1)	0 (-1, 1)
	Difference between 1st & 5th systolic BP measurements, mm Hg	256	22 (9)	975	22 (8)	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)	0 (-1, 1)
	Difference between 1st & 5th diastolic BP measurements, mm Hg	256	19 (9)	984	19 (8)	0 (-1, 1)	0 (-1, 1)	0 (-2, 1)	0 (-2, 1)

Grip strength (GS) was measured with the highest value for both dominant and non-dominant hands. Standardised scores were included for broad jump (BJ) and the shuttle run test (Run). The total of the standardised scores provided the physical function score. Blood pressure included pulse pressure as the difference between systolic and diastolic, and included values measured after the shuttle run test. Model 1 adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling).

Outcome		**CBHF**		**CHU**		**GEE Mean difference (95% CI) of CHU vs CBHF**			
Test	**Growth subtests**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Unadjusted**	**Adjusted difference Model 1 (Trial factors)**	**Adjusted difference Model 2 (Trial factors & contemporary covariates)**	**Adjusted difference Model 3 (Trial factors & baseline covariates)**
BIA	Reactance at 50 kHz, Ohms	261	73.5 (10.3)	981	71.7 (10.5)	-1.7 (-3.4, 0)	-1.7 (-3.3, 0)	-1.3 (-2.7, 0.2)	-1.3 (-2.7, 0.2)
	Resistance at 50 kHz, Ohms	262	833 (95)	986	830 (94)	-2.9 (-18.3, 12.5)	-2.9 (-18.3, 12.4)	-1.5 (-14.9, 11.9)	0 (-14.8, 14.7)

Table A6-7 Secondary Growth outcomes comparing CBHF and CHU

Bioimpedance (BIA) measured raw values of reactance and resistance in Ohms. Model 1 adjusted for trial factors (arm, study nurse, exact child age, calendar month recruited, temperature, sex). Model 2 adjusted for trial factors from Model 1 and contemporary factors (socioeconomic status, caregiver depression score (EPDS), household food insecurity (HFIAS), household religion, caregiver social support, caregiver gender norms, caregiver age, caregiver education, adversity score, children's books at home). Model 3 adjusted for trial factors from Model 1 and early-life factors (length for age Z-score (LAZ) at 18mo, birthweight, maternal baseline depression score (EPDS), household diet, maternal haemoglobin, socioeconomic status, facility birth, gender norms, and maternal years of schooling).

A6-7 Interaction analysis by child sex

Domain	Variable	P-value of interaction of HIV-exposure with child sex	GEE Coefficient for CHU vs CBHF Girls (95% CI)	GEE coefficient for CHU vs CBHF Boys (95% CI)
Cognitive function	Mental Processing Index	0.20	N/A	N/A
	School Achievement Test	0.99	N/A	N/A
	Plus EF test score	0.87	N/A	N/A
	Fine motor , sec	0.58	N/A	N/A
	Strengths and Difficulties Questionnaire	0.04	0.3 (-0.6, 1.2)	-1.2 (-0.2, -2.3)
	Child socioemotional score	0.05	0.1 (-0.0, 0.2)	-0.1 (-0.2, 0.0)
Physical function	Mean Grip Strength, Kg	0.47	N/A	N/A
	Mean Broad jump, m	0.61	N/A	N/A
	VO_2max, ml kg^{-1} min^{-1}	0.07	0.4 (-0.0, 0.8)	1.1 (0.5, 1.7)
	Diastolic BP, mm Hg	0.89	N/A	N/A
	Systolic BP, mm Hg	0.90	N/A	N/A
Growth and body composition	Height-for-age Z-score	0.37	N/A	N/A
	Weight-for-age Z-score	0.99	N/A	N/A
	BMI Z-score	0.30	N/A	N/A
	Knee-heel length	0.63	N/A	N/A
	Head circ, cm	0.72	N/A	N/A
	MUAC, cm	0.24	N/A	N/A
	Waist circ, cm	0.97	N/A	N/A
	Hip circ, cm	0.37	N/A	N/A
	Calf circ, m	0.08	0.3 (-0.0, 0.6)	-0.2 (-0.4, 0.2)
	Lean mass index	0.41	N/A	N/A
	Impedance Index	0.84	N/A	N/A
	Phase angle	0.45	N/A	N/A
	Total skinfold thicknesses, mm	0.19	N/A	N/A
	Peripheral skinfold thickness, mm	0.21	N/A	N/A
	Central skinfold thickness, mm	0.29	N/A	N/A

Domain	Variable	P-value of interaction of HIV-exposure with child sex	GEE Coefficient for CHU vs CBHF Girls (95% CI)	GEE coefficient for CHU vs CBHF Boys (95% CI)
	Hb, g dl^{-1}	0.30	N/A	N/A

Table A6-8 Results of subgroup analysis exploring interaction of child sex with HIV-exposure for SAHARAN toolbox outcomes.

For the subgroup analysis by child sex, if the p-value was greater than 0.1, the interaction was not considered significant, hence N/A (not applicable) was entered for the difference between boys and girls.

9.5 Chapter 7 appendix

A7-1 Baseline characteristics

Table A7-1Baseline characteristics of CHU by intervention arm for households and mothers

Baseline characteristics for SHINE Follow-up households for children born from mothers living without HIV (CHU) split by SHINE intervention arm. These include household demographics, socioeconomic status, electricity, water, sanitation, hygiene and maternal characteristics.

Domain	Baseline characteristic	SOC	IYCF	WASH	WASH+IYCF
Demographics	Caregiver assessed at 7 yr	247	250	247	248
	Child assessed at 7 yr	251	251	250	250
	Women completing baseline visit	224	224	240	238
Household size and wealth quintile	Size, median (IQR)	5.0 (3.0 ; 6.0)	5.0 (4.0 ; 7.0)	5.0 (3.0 ; 6.0)	5.0 (4.0 ; 6.0)
	Wealth quintiles				
	Lowest	48/223 (21.5%)	34/222 (15.3%)	46/237 (19.4%)	37/236 (15.7%)
	second	40/223 (17.9%)	35/222 (15.8%)	43/237 (18.1%)	50/236 (21.2%)
	Third	41/223 (18.4%)	58/222 (26.1%)	48/237 (20.3%)	40/236 (17.0%)
	Fourth	40/223 (17.9%)	46/222 (20.7%)	52/237 (21.9%)	62/236 (26.3%)
	Fifth	54/223 (24.2%)	49/222 (22.1%)	48/237 (20.3%)	47/236 (19.9%)
Electricity	Electricity to home	7/222(3.2%)	11/221 (5.0%)	9/238 (3.8%)	4/237 (1.7%)
	Generator	8/222 (3.6%)	9/221 (4.1%)	6/238 (2.5%)	9/237 (3.8%)
	Solar	148/222 (66.7%)	156/221 (70.6%)	165/238 (69.3%)	165/237 (69.6%)
	Inverter	4/222 (1.8%)	3/221 (1.4%)	4/238 (1.7%)	2/237 (0.8%)
	no other type	62/222 (27.9%)	53/221 (24.0%)	63/238 (26.5%)	61/237 (25.7%)
Sanitation	Any latrine	73/222 (32.9%)	88/220 (40.0%)	96/234 (41.0%)	88/227 (38.8%)
	Improved latrine	60/222 (27.0%)	73/220 (33.2%)	83/233 (35.6%)	75/227 (33.0%)
Water	Main source of household drinking water is improved	148/222 (66.7%)	155/220 (70.5%)	154/233 (66.1%)	163/229 (71.2%)
	Treat drinking water to make it safer	39/221 (17.7%)	35/219 (16.0%)	36/232 (15.5%)	19/227 (33.0%)
	1 way walk time to fetch water	10.0 (5.0 ; 20.0)	10.0 (5.0 ; 20.0)	10.0 (5.0 ; 20.0)	10.0 (5.0 ; 20.0)
	Per capita water volume	6.7 (4.2 ; 10.0)	6.7 (4.0 ; 10.0)	6.7 (5.0 ; 10.0)	6.7 (4.4 ; 10.0)
Hygiene	Handwashing station with water	16/216 (7.4%)	11/214 (5.1%)	36/229 (15.7%)	38/221 (17.2%)
	Improved floor	116/217 (53.5%)	115/220 (52.3%)	137/233 (58.8%)	119/234 (8.4%)
	Chickens yes/no	177/224 (79.0%)	187/222 (84.2%)	190/236 (80.5%)	199/237 (84.0%)

Domain	Baseline characteristic	SOC	IYCF	WASH	WASH+IYCF
	Faeces observed in yard	75/239 (31.4%)	92/242 (38.0%)	87/240 (36.3%)	69/241 (28.6%)
Diet quality and food security	Household meets minimum dietary diversity score	76/213 (35.7%)	87/214 (40.7%)	83/227 (36.6%)	85/230 (37.0%)
	Coping Strategies index	1.0 (0.0 ; 6.0)	0.0 (0.0 ; 5.0)	0.0 (0.0 ; 5.0)	1.0 (0.0 ; 6.0)
Maternal characteristics	Age (yr, SD)d	25.3 (6.3)	25.5 (6.0)	25.8 96.8)	26.2 (5.9)
	Maternal height	159.9 (5.9)	160.1 (6.4)	159.6 (5.6%)	159.9 (5.9)
	Maternal MUAC	26.2 (3.1)	26.6 (3.2)	26.8 (3.6)	26.7 (3.1)
	Maternal Schooling	9.7 (1.8)	9.9 (1.6)	9.6 (1.6)	9.6 (1.7)
	Parity	2.0 (1.0 ; 3.0)	1.0 (1.0 ; 2.0)	1.0 (1.0 ; 3.0)	2.0 (1.0 ; 3.0)
	Married	226/240 (51.0%)	219/232 (94.4%)	220/231 (95.2%)	228/236 (96.6%)
	Employed	10/223 (4.5%)	20/222 (9.0%)	24/238 (10.1%)	16/237 (6.8%)
	Religion				
	Apostolic	123/241 (51.0%)	111/233 (47.6%)	112/234 (47.9%)	110/237 (46.4%)
	Other Christian	101/241 (41.9%)	107/233 (45.9%)	90/234 (38.5%)	100/237 (42.2%)
	Other religion	17/241 (7.1%)	15/233 (6.4%)	32/234 (13.7%)	27/237 (11.4%)
Maternal capabilities	Gender norm attitudes	2.7 (1.7 ; 3.2)	2.7 (1.7 ; 3.2)	1.7 (1.5 ; 3.0)	2.0 (1.5 ; 3.0)
	Perceived social support	3.5 (3.1 ; 3.9)	3.7 (3.1 ; 4.1)	3.6 (3.2 ; 3.1)	3.7 (3.2 ; 4.0)

Domain	Child characteristics	SOC	IYCF	WASH	WASH+IYCF
	Female	120/251 (47.8%)	121/251 (48.2%)	141/250 (56.4%)	129/250 (51.6%)
Birth	Birthweight	3.1 (0.5)	3.1 (0.5)	3.1 (0.5)	3.1 (0.4)
	Low birthweight	25/237 (10.6%)	20/240 (8.3%)	28/242 (11.6%)	17/238 (7.1%)
	Institutional delivery	213/238 (89.5%)	215/232 (92.7%)	211/235 (89.8%)	216/230 (93.9%)
	Vaginal delivery	235/246 (95.5%)	224/236 994.9%)	231/245 (94.3%)	219/238 (92.0%)
18 month measurements	LAZ at 18 months	-1.6 (1.0)	-1.4 (1.1)	-1.6 (1.0)	-1.5 (1.0)
	Stunted at 18 months	87/249 (34.9%)	61/249 (24.5%)	80/247 32.4%)	70/248 (28.2%)
	WAZ at 18 months	-0.8 (1.0)	-0.6 (1.0)	-0.8 (1.0)	-0.8 (0.9)
	headcirc at 18 months	-0.2 (1.0)	-0.2 (1.0)	-03 (1.1)	-0.2 (1.1)
	MUAC at 18 months	0.2 (0.9)	0.2 (0.9)	-0.01 (0.9)	0.1 (0.8)
24 month measurements	MDAT total at 24 months, n, mean, SD	91.1 (11.0)	93.1 (9.2)	90/7 (9.9)	92.7 (10.0)
	Mcarthur Bates at 24 months, n, mean, SD	60.5 (21.0)	64.1 (18.1)	61.1 (20.8)	63.0 (20.4)

Table A7-2 Baseline characteristics of CHU by intervention arm for children

Baseline characteristics for SHINE Follow-up children born from mothers living without HIV (CHU) split by SHINE intervention arm. This includes measurements at birth, 18 months and 24 month.

A7-2 Interaction of SHINE interventions with child sex

Table A7-3 Exploring the interaction between child sex and trial intervention arm on school-age SAHARAN toolbox outcomes.

Child domain	**School-age child outcome**	**Intervention**	**P-value for interaction of intervention with child sex**	**GEE Coefficient for Girls (95% CI)**	**p-value**	**GEE coefficient for Boys (95% CI)**	**p-value**
Cognitive function (no significant interaction between WASH & IYCF interventions)	Mental Processing Index	IYCF	0.062	0.77 (-1.52, 3.06)	0.510	-2.26 (-4.28, -0.24)	0.028
		WASH	0.280	N/A		N/A	
	School Achievement Test	IYCF	0.528	N/A		N/A	
		WASH	0.773	N/A		N/A	
	Plus EF test score	IYCF	0.091	4.37 (-0.06, 8.80)	0.053	-1.62 (-6.42, 3.17)	0.508
		WASH	0.132	N/A		N/A	
	Fine motor , sec	IYCF	0.227	N/A		N/A	
		WASH	0.355	N/A		N/A	
	Strengths and Difficulties Questionnaire	IYCF	0.628	N/A		N/A	
		WASH	0.905	N/A		N/A	
	Child socioemotional score	IYCF	0.795	N/A		N/A	
		WASH	0.950	N/A		N/A	
Physical function (interaction between WASH & IYCF interventions)	Mean Grip Strength, Kg	IYCF	0.025	-0.23 (-0.62, 0.16)	0.251	0.53 (0.19, 0.87)	0.002
		WASH	0.292	N/A		N/A	
		IYCF&WASH	0.102	N/A		N/A	
	Mean Broad jump, m	IYCF	0.553	N/A		N/A	
		WASH	0.760	N/A		N/A	
		IYCF&WASH	0.895	N/A		N/A	
	VO2max (Cardiovascular fitness)	IYCF	0.079	-0.47 (-0.96, 0.01)	0.057	0.15 (-0.48, 0.77)	0.644
		WASH	0.126	N/A		N/A	
		IYCF&WASH	0.038	0.58	0.025	-0.29	0.324

Child domain	School-age child outcome	Intervention	P-value for interaction of intervention with child sex	GEE Coefficient for Girls (95% CI)	p-value	GEE coefficient for Boys (95% CI)	p-value
				(0.07, 1.08)		(-0.87, 0.29)	
	Diastolic BP, mm Hg	IYCF	0.917	N/A		N/A	
		WASH	0.965	N/A		N/A	
		IYCF&WASH	0.999	N/A		N/A	
	Systolic BP, mm Hg	IYCF	0.485	N/A		N/A	
		WASH	0.997	N/A		N/A	
		IYCF&WASH	0.590	N/A		N/A	
Growth and Body composition (no significant interaction between WASH & IYCF interventions)	Height-for-age Z-score	IYCF	0.251	N/A		N/A	
		WASH	0.836	N/A		N/A	
	Weight-for-age Z-score	IYCF	0.961	N/A		N/A	
		WASH	0.694	N/A		N/A	
	BMI Z-score	IYCF	0.210	N/A		N/A	
		WASH	0.831	N/A		N/A	
	Knee-heel length	IYCF	0.111	N/A		N/A	
		WASH	0.944	N/A		N/A	
	Head circ, cm	IYCF	0.402	N/A		N/A	
		WASH	0.634	N/A		N/A	
	MUAC, cm	IYCF	0.457	N/A		N/A	
		WASH	0.478	N/A		N/A	
	Waist circ, cm	IYCF	0.641	N/A		N/A	
		WASH	0.779	N/A		N/A	
	Hip circ, cm	IYCF	0.254	N/A		N/A	
		WASH	0.941	N/A		N/A	
	Calf circ, m	IYCF	0.524	N/A		N/A	
		WASH	0.799	N/A		N/A	
	Lean mass index, $Ohms^{-1}$	IYCF	0.349	N/A		N/A	
		WASH	0.231	N/A		N/A	
	Impedance Index, m^2 $Ohms^{-1}$	IYCF	0.993	N/A		N/A	
		WASH	0.531	N/A		N/A	
	Phase angle, degrees	IYCF	0.566	N/A		N/A	
		WASH	0.739	N/A		N/A	
	Total skinfold thicknesses, mm	IYCF	0.585	N/A		N/A	

Child domain	School-age child outcome	Intervention	P-value for interaction of intervention with child sex	GEE Coefficient for Girls (95% CI)	p-value	GEE coefficient for Boys (95% CI)	p-value
		WASH	0.999	N/A		N/A	
	Peripheral skinfold thickness, mm	IYCF	0.385	N/A		N/A	
		WASH	0.823	N/A		N/A	
	Central skinfold thickness, mm	IYCF	0.986	N/A		N/A	
		WASH	0.924	N/A		N/A	
	Hb, g dl^{-1}	IYCF	0.976	N/A		N/A	
		WASH	0.121	N/A		N/A	

A7-4 Impact of SHINE interventions on detailed secondary Cognitive Outcomes

KABC-II subtests and subdomains

Table A7-4 The effect of the early-life SHINE interventions on the individual subtests and domains within the Kaufmann assessment battery for children (KABC-II).

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Kaufmann Assessment Battery for Children 2nd edition (KABC-II) subtests.	Atlantis	SoC	246	6 (2)	No IYCF	493	6 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	6 (2)	IYCF	497	6 (3)	0 (-1, 0)	0.103	980	0 (-1, 0)	0.073
		WASH	247	6 (2)	No WASH	496	6 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	6 (3)	WASH	494	6 (2)	0 (0, 0)	0.503	980	0 (0, 0)	0.697
	Story Completion	SoC	246	5 (2)	No IYCF	493	5 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	5 (2)	IYCF	497	5 (2)	0 (0, 0)	0.964	980	0 (0, 0)	0.608
		WASH	247	5 (2)	No WASH	496	5 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	4 (2)	WASH	494	4 (2)	0 (0, 0)	0.653	980	0 (0, 0)	0.684
	Number recall	SoC	246	7 (2)	No IYCF	493	7 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	8 (2)	IYCF	497	7 (2)	0 (0, 0)	0.736	980	0 (0, 0)	0.718

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
		WASH	247	7 (2)	No WASH	496	8 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	7 (2)	WASH	494	7 (2)	0 (0, 0)	0.100	980	0 (0, 0)	0.206
	Atlantis Delayed	SoC	246	7 (2)	No IYCF	493	7 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	7 (2)	IYCF	**497**	**7 (2)**	**0 (-1, 0)**	**0.010**	**980**	**0 (-1, 0)**	**0.011**
		WASH	247	7 (2)	No WASH	496	7 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	7 (2)	WASH	494	7 (2)	0 (0, 0)	0.791	980	0 (0, 0)	0.981
	Rover	SoC	246	7 (2)	No IYCF	493	7 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	7 (2)	IYCF	497	7 (2)	0 (-1, 0)	0.382	980	0 (-1, 0)	0.264
		WASH	247	7 (2)	No WASH	496	7 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	7 (2)	WASH	494	7 (2)	0 (0, 0)	0.891	980	0 (0, 0)	0.805
	Triangle	SoC	246	4 (2)	No IYCF	493	4 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	4 (2)	IYCF	497	4 (2)	0 (0, 0)	0.381	980	0 (0, 0)	0.415
		WASH	247	4 (2)	No WASH	496	4 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	4 (2)	WASH	494	4 (2)	0 (0, 0)	0.633	980	0 (0, 0)	0.385
	Word Order	SoC	246	6 (2)	No IYCF	493	6 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	6 (2)	IYCF	497	6 (2)	0 (0, 0)	0.071	980	0 (0, 0)	0.063

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
		WASH	247	6 (2)	No WASH	496	6 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	6 (2)	WASH	494	6 (2)	0 (0, 0)	0.613	980	0 (0, 0)	0.497
	Pattern Reasoning	SoC	246	6 (3)	No IYCF	493	6 (3)	0.0 (ref)			0.0 (ref)	
		IYCF	250	6 (2)	IYCF	497	6 (3)	0 (0, 0)	0.858	980	0 (0, 0)	0.954
		WASH	247	6 (2)	No WASH	496	6 (3)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	6 (3)	WASH	494	6 (3)	0 (-1, 0)	0.282	980	0 (-1, 0)	0.382
											0.0 (ref)	
KABC-II cognitive sub-domains	Learn	SoC	246	14 (4)	No IYCF	493	14 (4)	0.0 (ref)		980	-1 (-1, 0)	0.022
		IYCF	250	13 (4)	IYCF	497	13 (4)	-1 (-1, 0)	0.030		0.0 (ref)	
		WASH	247	14 (4)	No WASH	496	13 (4)	0.0 (ref)		980	0 (-1, 0)	0.721
		WASH & IYCF	247	13 (4)	WASH	494	13 (4)	0 (-1, 0)	0.494		0.0 (ref)	
	Planning	SoC	246	11 (4)	No IYCF	493	11 (4)	0.0 (ref)		980	0 (-1, 0)	0.713
		IYCF	250	11 (3)	IYCF	497	11 (3)	0 (0, 0)	0.995		0.0 (ref)	
		WASH	247	10 (4)	No WASH	496	11 (4)	0.0 (ref)		980	0 (-1, 0)	0.376
		WASH & IYCF	247	10 (4)	WASH	494	10 (4)	0 (-1, 0)	0.243		0.0 (ref)	
	Simultaneous	SoC	246	11 (4)	No IYCF	493	11 (4)	0.0 (ref)		980	0 (-1, 1)	0.874

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
		IYCF	250	11 (4)	IYCF	497	11 (3)	0 (-1, 1)	0.986		0.0 (ref)	
		WASH	247	11 (4)	No WASH	496	11 (4)	0.0 (ref)		980	0 (-1, 0)	0.512
		WASH & IYCF	247	11 (3)	WASH	494	11 (4)	0 (-1, 0)	0.700		0.0 (ref)	
	Sequential	SoC	246	13 (4)	No IYCF	485	3.7 (0.7)	0.0 (ref)		980	0 (-1, 0)	0.265
		IYCF	250	13 (4)	IYCF	488	3.7 (0.7)	0 (-1, 0)	0.328		0.0 (ref)	
		WASH	247	13 (4)	No WASH	489	3.7 (0.7)	0.0 (ref)		980	0 (-1, 0)	0.205
		WASH & IYCF	247	13 (4)	WASH	484	3.7 (0.7)	0 (-1, 0)	0.210		0.0 (ref)	

School achievement test (SAT)

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
School achievement test domains	*Numeracy*	SoC	246	19 (6)	No IYCF	493	19 (6)	0.0 (ref)			0.0 (ref)	
		IYCF	250	18 (6)	IYCF	497	18 (6)	0 (-1, 1)	0.433	980	0 (-1, 1)	0.462
		WASH	247	18 (6)	No WASH	496	19 (6)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	18 (6)	WASH	494	18 (6)	-1 (-2, 0)	0.162	980	-1 (-2, 0)	0.163
	Reading	SoC	246	14 (14)	No IYCF	493	14 (14)	0.0 (ref)			0.0 (ref)	
		IYCF	250	13 (13)	IYCF	497	13 (13)	-1 (-3, 1)	0.332	980	-1 (-3, 1)	0.376
		WASH	247	14 (14)	No WASH	496	14 (13)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	12 (13)	WASH	494	13 (13)	-1 (-3, 1)	0.476	980	-1 (-3, 2)	0.585
	Writing	SoC	246	14 (10)	No IYCF	493	14 (10)	0.0 (ref)			0.0 (ref)	
		IYCF	250	14 (10)	IYCF	497	14 (10)	0 (-2, 1)	0.738	980	0 (-2, 1)	0.822
		WASH	247	14 (10)	No WASH	496	14 (10)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	13 (9)	WASH	494	14 (10)	-1 (-2, 1)	0.332	980	-1 (-2, 1)	0.364

Table A7-5 The effect of the early-life SHINE interventions on the individual domains within the School achievement test (SAT).

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Plus-EF

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Plus EF subtest scores	MSIT	SoC	240	25 (10)	No IYCF	486	24 (11)	0.0 (ref)			0.0 (ref)	
		IYCF	248	25 (11)	IYCF	492	25 (11)	1 (-1, 2)	0.343	968	1 (-1, 3)	0.218
		WASH	246	24 (11)	No WASH	488	25 (10)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	244	24 (11)	WASH	490	24 (11)	-1 (-3, 0)	0.124	968	-1 (-3, 0)	0.136
	Stars and Flowers	SoC	240	43 (9)	No IYCF	486	43 (9)	0.0 (ref)			0.0 (ref)	
		IYCF	248	43 (9)	IYCF	492	43 (9)	0 (-1, 1)	0.970	968	0 (-1, 1)	0.929
		WASH	246	43 (9)	No WASH	488	43 (9)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	244	42 (9)	WASH	490	42 (9)	-1 (-2, 0)	0.214	968	-1 (-2, 0)	0.151
	Flanker	SoC	240	47 (12)	No IYCF	486	47 (12)	0.0 (ref)			0.0 (ref)	
		IYCF	248	47 (11)	IYCF	492	48 (11)	1 (0, 2)	0.185	968	1 (0, 2)	0.193
		WASH	246	46 (12)	No WASH	488	47 (12)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	244	48 (11)	WASH	490	47 (12)	0 (-2, 1)	0.752	968	0 (-2, 1)	0.661

Table A7-6 The effect of the early-life SHINE interventions on the individual domains within the PlusEF executive function test.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Fine motor function (finger tapping)

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Fine motor (Finger tapping time), seconds	Dominant Hand	SoC	244	23.1 (6.5)	No IYCF	491	23 (6.3)	0.0 (ref)			0.0 (ref)	
		IYCF	250	23.8 (7.3)	IYCF	495	23.7 (7.3)	0.7 (-0.3, 1.6)	0.168	976	0.6 (-0.3, 1.5)	0.169
		WASH	247	22.8 (6)	No WASH	494	23.5 (6.9)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	245	23.6 (7.2)	WASH	492	23.2 (6.6)	-0.3 (-1.2, 0.6)	0.544	976	-0.6 (-1.5, 0.4)	0.22
	Non- dominant hand	SoC	244	24.4 (7.0)	No IYCF	491	24.4 (6.8)	0.0 (ref)			0.0 (ref)	
		IYCF	250	25.6 (7.6)	IYCF	495	25.2 (7.3)	0.8 (-0.1, 1.7)	0.069	976	0.8 (-0.1, 1.7)	0.066
		WASH	247	24.3 (6.5)	No WASH	494	25.0 (7.3)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	245	24.8 (7.1)	WASH	492	24.6 (6.8)	-0.4 (-1.3, 0.5)	0.346	976	-0.7 (-1.6, 0.2)	0.151

Table A7-7 The effect of the early-life SHINE interventions on dominant and non-dominant hands within the finger tapping test which measured fine motor function.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Strengths and difficulties Questionnaire and Child Socioemotional score

Table A7-8: The effect of the early-life SHINE interventions on socioemotional function measured by the Caregiver Strengths and Difficulties Questionnaire (SDQ).

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Strengths and Difficulties Questionnaire sub-scales	Emotional Problems Scale	SoC	245	2 (2)	No IYCF	492	2 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	2 (2)	IYCF	497	2 (2)	0 (-1, 0)	0.168	979	0 (-1, 0)	0.223
		WASH	247	2 (2)	No WASH	495	2 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	2 (2)	WASH	494	2 (2)	**0 (-1, 0)**	**0.014**	**979**	**0 (-1, 0)**	**0.031**
	Conduct Problems Scale	SoC	245	2 (2)	No IYCF	492	2 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	2 (2)	IYCF	497	2 (2)	0 (0, 0)	0.163	979	0 (0, 0)	0.151
		WASH	247	2 (2)	No WASH	495	2 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	2 (2)	WASH	494	2 (2)	0 (0, 0)	0.115	979	0 (-1, 0)	0.088
	Hyperactivity Scale	SoC	245	4 (2)	No IYCF	492	4 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	4 (2)	IYCF	497	4 (2)	0 (0, 0)	0.323	979	0 (-1, 0)	0.248
		WASH	247	4 (2)	No WASH	495	4 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	3 (2)	WASH	494	3 (2)	0 (-1, 0)	0.053	979	0 (-1, 0)	0.089

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
	Peer Problems Scale	SoC	245	1 (2)	No IYCF	492	1 (1)	0.0 (ref)			0.0 (ref)	
		IYCF	250	1 (1)	IYCF	497	1 (1)	0 (0, 0)	0.157	979	0 (0, 0)	0.387
		WASH	247	1 (1)	No WASH	495	1 (1)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	1 (1)	WASH	494	1 (1)	0 (0, 0)	0.648	979	0 (0, 0)	0.27
	Prosocial Scale	SoC	245	8 (2)	No IYCF	492	8 (2)	0.0 (ref)			0.0 (ref)	
		IYCF	250	8 (2)	IYCF	497	8 (2)	0 (0, 0)	0.239	979	0 (0, 0)	0.272
		WASH	247	8 (2)	No WASH	495	8 (2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	247	8 (2)	WASH	494	8 (2)	0 (0, 0)	0.161	979	0 (0, 0)	0.49

Child socioemotional function (removing food security question)

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Child Socioemtional Questionnaire	Child Socioemotional Questionnaire without food security question	SoC	242	4 (1)	No IYCF	485	4 (1)	0.0 (ref)			0.0 (ref)	
		IYCF	247	4 (1)	IYCF	488	4 (1)	0 (0,0)	0.705	963	0 (0, 0)	0.84
		WASH	243	4 (1)	No WASH	489	4 (1)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	241	4 (1)	WASH	484	4 (1)	0 (0,0)	0.255	963	0 (0, 0)	0.251

Table A7-9: The effect of the early-life SHINE interventions on socioemotional function measured by the Child Socioemotional function removing a question on food security.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

A7-5 Impact of SHINE interventions on detailed secondary Physical Outcomes

Grip strength and standardised scores

Table A7-10: The effect of the early-life SHINE interventions on detailed secondary physical outcomes.

The total physical function score were calculated by the sum of the standardised scores. SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Outcome	Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
Grip strength Dominant Hand, Kg	SoC	246	10.6 (1.9)	0.0 (ref)			0.0 (ref)	
	IYCF	250	10.9 (2.1)	**0.3 (0.1, 0.5)**	**0.008**	**980**	**0.3 (0.1, 0.5)**	**0.007**
	WASH	247	10.9 (2.1)	0.2 (-0.2, 0.5)	0.303	980	0.1 (-0.2, 0.4)	0.532
	WASH & IYCF	247	10.8 (2)	0.1 (-0.2, 0.4)	0.398	980	0.2 (0, 0.4)	0.117
Grip Strength Non-dominant Hand, Kg	SoC	246	10.5 (2)	0.0 (ref)			0.0 (ref)	
	IYCF	250	10.7 (2.2)	0.2 (-0.1, 0.5)	0.115	980	0.2 (-0.1, 0.5)	0.212
	WASH	247	10.6 (2.3)	0.1 (-0.3, 0.4)	0.725	980	0 (-0.3, 0.4)	0.862
	WASH & IYCF	247	10.5 (2)	0 (-0.3, 0.3)	0.893	980	0 (-0.3, 0.3)	0.895
Standardised Grip strength (a)	SoC	246	0 (0.9)	0.0 (ref)			0.0 (ref)	

Outcome	Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
	IYCF	250	0.1 (1)	**0.1 (0, 0.3)**	**0.032**	980	0.1 (0, 0.2)	0.056
	WASH	247	0.1 (1)	0.1 (-0.1, 0.2)	0.421	980	0 (-0.1, 0.2)	0.800
	WASH & IYCF	247	0 (1)	0 (-0.1, 0.2)	0.734	980	0 (-0.1, 0.1)	0.616
Standardised Broad jump (b)	SoC	245	0 (0.9)	0.0 (ref)			0.0 (ref)	
	IYCF	249	0 (1)	0 (-0.2, 0.1)	0.683	977	-0.1 (-0.2, 0.1)	0.517
	WASH	246	0.1 (0.9)	0 (-0.2, 0.2)	0.922	977	0 (-0.2, 0.2)	0.993
	WASH & IYCF	247	0.1 (1)	0 (-0.2, 0.2)	0.899	977	0 (-0.2, 0.2)	0.875
Standardised VO_2max (c)	SoC	245	0.2 (1)	0.0 (ref)			0.0 (ref)	
	IYCF	248	0 (0.9)	-0.1 (-0.3, 0.1)	0.183	975	-0.2 (-0.3, 0)	0.104
	WASH	247	0 (1.1)	-0.2 (-0.4, 0)	0.101	975	-0.1 (-0.3, 0.1)	0.380
	WASH & IYCF	246	0.1 (1)	-0.1 (-0.2, 0.1)	0.558	975	0 (-0.2, 0.2)	0.758
Standardised physical function score (= a + b +c)	SoC	244	0.2 (2)	0.0 (ref)			0.0 (ref)	
	IYCF	248	0.1 (2.1)	-0.1 (-0.4, 0.3)	0.746	-0.1 (-0.5, 0.2)	0.523	978
	WASH	246	0.1 (2.1)	-0.1 (-0.5, 0.4)	0.708	0 (-0.4, 0.5)	0.863	978
	WASH & IYCF	246	0.1 (2)	0.0 (-0.4, 0.4)	0.913	0 (-0.4, 0.4)	0.98	978

Blood pressure

Table A7-11 The effect of the early-life SHINE interventions on blood pressure and its recovery after the Shuttle run tests.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Outcome	Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
Resting pulse pressure, mm Hg	SoC	245	34.8 (7.8)	0.0 (ref)			0.0 (ref)	
	IYCF	250	34.4 (7.4)	-0.5 (-1.6, 0.6)	0.396	978	-0.3 (-1.1, 0.6)	0.558
	WASH	246	34.7 (7.5)	0 (-1, 1)	0.968	978	0 (-0.9, 0.9)	0.998
	WASH & IYCF	247	34.8 (7.2)	-0.1 (-1.2, 1.1)	0.927	978	-0.2 (-1.5, 1.1)	0.751
Systolic blood pressure 1 minute after shuttle run test, mm Hg	SoC	242	127.1 (10)	0.0 (ref)			0.0 (ref)	
	IYCF	247	126.9 (10.2)	-0.2 (-2.1, 1.7)	0.830	966	0 (-1.9, 1.9)	0.981
	WASH	245	125.2 (11.6)	**-1.9 (-3.7, -0.2)**	**0.028**	966	-1.5 (-3.1, 0.1)	0.072
	WASH & IYCF	242	126.9 (10.4)	-0.3 (-2.1, 1.6)	0.786	966	-0.3 (-2.1, 1.5)	0.764
Diastolic Blood pressure 1 minute after shuttle run test, mm Hg	SoC	245	85.9 (10.3)	0.0 (ref)			0.0 (ref)	
	IYCF	248	85.5 (11.3)	-0.5 (-2.1, 1.2)	0.600	975	-0.5 (-2.2, 1.2)	0.574
	WASH	246	85.9 (12.2)	0.1 (-1.6, 1.8)	0.932	975	0.3 (-1.4, 2)	0.727
	WASH & IYCF	246	85.8 (11.9)	0.1 (-1.8, 2)	0.927	975	0 (-1.8, 1.9)	0.972

Outcome	Treatment group	N	Mean (SD)	Unadjusted diff (95%CI)	p	N Adj	Adjusted diff (95%CI)	p
Exercise pulse pressure, mm Hg	SoC	245	40.2 (8.6)	0.0 (ref)			0.0 (ref)	
	IYCF	248	40.4 (8.6)	0.1 (-1, 1.3)	0.796	975	0.2 (-0.9, 1.3)	0.763
	WASH	246	39.3 (8.8)	-1 (-1.9, 0)	0.052	975	-0.4 (-1.5, 0.7)	0.470
	WASH & IYCF	246	40 (8.5)	-0.2 (-1.4, 1)	0.739	975	-0.3 (-1.3, 0.6)	0.474
Change in systolic blood pressure between 1st and 5th readings after Shuttle run test, mm Hg	SoC	242	22.1 (7.8)	0.0 (ref)			0.0 (ref)	
	IYCF	247	22.3 (8.4)	0.1 (-1.4, 1.7)	0.857	965	0.1 (-1.3, 1.5)	0.924
	WASH	244	21.7 (8.2)	-0.4 (-1.7, 0.9)	0.562	965	-0.3 (-1.4, 0.8)	0.646
	WASH & IYCF	242	21.4 (8.4)	-0.7 (-2.1, 0.6)	0.288	965	-0.6 (-1.5, 0.4)	0.235
Change in diastolic blood pressure between 1st and 5th readings after Shuttle run test, mm Hg	SoC	245	18 (7)	0.0 (ref)			0.0 (ref)	
	IYCF	248	18 (8.3)	0 (-1.2, 1.2)	0.957	974	-0.2 (-1.4, 0.9)	0.679
	WASH	245	19.9 (8.5)	**2 (0.5, 3.4)**	**0.008**	**974**	**2.1 (0.7, 3.4)**	**0.003**
	WASH & IYCF	246	18.1 (8.3)	0.2 (-1.1, 1.4)	0.812	974	0.4 (-0.6, 1.4)	0.448

A7-6 Impact of SHINE interventions on detailed secondary Growth Outcomes

Bioimpedance outcomes

Outcome Domain	Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Bioimpedance outcomes	Reactance at 50 kHz, Ohms	SoC	243	72.7 (11.6)	No IYCF	489	72.1 (10.7)	0.0 (ref)			0.0 (ref)	
		IYCF	247	71.6 (10.9)	IYCF	492	71.4 (10.3)	-0.8 (-2.3, 0.7)	0.276	971	0.1 (-1.3, 1.6)	0.858
		WASH	246	71.6 (9.7)	No WASH	490	72.1 (11.2)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	245	71.1 (9.7)	WASH	491	71.4 (9.7)	-0.6 (-2.1, 0.9)	0.469	971	-0.7 (-2.1, 0.6)	0.263
	Resistance at 50 kHz, Ohms	SoC	244	837.3 (97.8)	No IYCF	491	833.2 (98.5)	0.0 (ref)			0.0 (ref)	
		IYCF	250	828.2 (95.5)	IYCF	495	826.4 (88.5)	-6.9 (-19, 5.1)	0.260	976	2.1 (-8, 12.2)	0.685
		WASH	247	829.2 (99.1)	No WASH	494	832.7 (96.7)	0.0 (ref)			0.0 (ref)	
		WASH & IYCF	245	824.6 (80.8)	WASH	492	826.9 (90.4)	-5.5 (-17.6, 6.5)	0.368	976	-5.5 (-16, 5)	0.306

Table A7-12 The effect of the early-life SHINE interventions on bioimpedance resistance and reactance at 50 kHz.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

A7-7 Post-hoc analysis of absolute height

Height was not pre-specified in the statistical analysis plan as an outcome. However, it was explored as an outcome to see if any there was any evidence of an effect of the early-life outcomes on absolute height.

Detailed Outcome	Treatment group	N	Mean (SD)	Treatment Group	N	Mean (SD)	Unadjusted diff (95% CI)	p	N Adj	Adjusted diff (95%CI)	p
Height, cm	SoC	246	119.7 (4.7)	No IYCF	493	119.9 (4.7)	0.0 (ref)			0.0 (ref)	
	IYCF	250	120.5 (4.9)	IYCF	497	120.3 (5.1)	0.4 (-0.2, 1.0)	0.197	980	0.3 (-0.2, 0.9)	0.226
	WASH	247	120.2 (4.7)	No WASH	496	120.1 (4.8)	0.0 (ref)			0.0 (ref)	
	WASH & IYCF	247	120.2 (5.2)	WASH	494	120.2 (5)	0.1 (-0.5, 0.7)	0.675	980	0.1 (-0.5, 0.6)	0.745

Table A7-13 Post-hoc analysis of the effect of the early-life SHINE interventions on absolute height.

SoC: Standard of Care arm, IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

A7-8 Post-hoc analysis exploring the interaction with stunting at 18 months

Table A7-14 Post hoc analysis exploring the interaction of SHINE intervention with child stunting at 18 months

IYCF: Infant and Young Child Feeding arm, WASH: Water, Sanitation and Hygiene arm WASH & IYCF: Combined arm

Domain	Variable	Treatment Group	P-value of interaction of intervention with child stunting at 18 months	GEE Coefficient for Stunted at 18 months (95% CI)	p-value	GEE coefficient for Not stunted at 18 months (95% CI)	p-value
Cognitive function	Mental Processing Index	IYCF	0.158	N/A		N/A	
		WASH	0.403	N/A		N/A	
	School Achievement Test	IYCF	0.611	N/A		N/A	
		WASH	0.036	**-7.58 (-14.5, -0.66)**	**0.032**	-0.01 (-5.58, 5.57)	0.998
	Plus EF test score	IYCF	0.288	N/A		N/A	
		WASH	0.069	-6.32 (-11.88, -0.77)	0.026	-0.65 (-4.39, 3.09)	0.732
	Fine motor , sec	IYCF	0.909	N/A		N/A	
		WASH	0.005	1.71 (0.14, 3.29)	0.033	-1.19 (-2.28, -0.10)	0.032
	Strengths and Difficulties Questionnaire	IYCF	0.920	N/A		N/A	
		WASH	0.528	N/A		N/A	
	Child socioemotional score	IYCF	0.734	N/A		N/A	
		WASH	0.214	N/A		N/A	
Physical function	Mean Grip Strength, Kg	IYCF	0.661	N/A		N/A	
		WASH	0.305	N/A		N/A	
		IYCF&WASH	0.594	N/A		N/A	
	Mean Broad jump, m	IYCF	0.923	N/A		N/A	
		WASH	0.776	N/A		N/A	
		IYCF&WASH	0.030	**-3.50**	**0.024**	1.45	0.294

Domain	Variable	Treatment Group	P-value of interaction of intervention with child stunting at 18 months	GEE Coefficient for Stunted at 18 months (95% CI)	p-value	GEE coefficient for Not stunted at 18 months (95% CI)	p-value
				(-6.53, -0.47)		(-1.26, 4.16)	
	VO2max (Cardiovascular fitness)	IYCF	0.058	0.46 (-0.28, 1.20)	0.223	-0.38 (-0.89, 0.13)	0.142
		WASH	0.074	**-0.86 (-1.50, -0.23)**	**0.008**	-0.09 (-0.70, 0.52)	0.773
		IYCF&WASH	0.148	N/A		N/A	
	Diastolic BP, mm Hg	IYCF	0.541	N/A		N/A	
		WASH	0.218	N/A		N/A	
		IYCF&WASH	0.373	N/A		N/A	
	Systolic BP, mm Hg	IYCF	0.650	N/A		N/A	
		WASH	0.554	N/A		N/A	
		IYCF&WASH	0.399	N/A		N/A	
Growth and Body composition	Height-for-age Z-score	IYCF	0.390	N/A		N/A	
		WASH	0.904	N/A		N/A	
	Weight-for-age Z-score	IYCF	0.897	N/A		N/A	
		WASH	0.227	N/A		N/A	
	BMI Z-score	IYCF	0.568	N/A		N/A	
		WASH	0.073	0.14 (-0.06, 0.33)	0.167	-0.10 (-0.25, 0.05)	0.198
	Knee-heel length	IYCF	0.173	N/A		N/A	
		WASH	0.255	N/A		N/A	
	Head circ, cm	IYCF	0.362	N/A		N/A	
		WASH	0.041	0.16 (-0.13, 0.46)	0.276	-0.17 (-0.36, 0.03)	0.100
	MUAC, cm	IYCF	0.549	N/A		N/A	
		WASH	0.384	N/A		N/A	
	Waist circ, cm	IYCF	0.728	N/A		N/A	
		WASH	0.806	N/A		N/A	
	Hip circ, cm	IYCF	0.907	N/A		N/A	
		WASH	0.705	N/A		N/A	
	Calf circ, m	IYCF	0.487	N/A		N/A	

Domain	Variable	Treatment Group	P-value of interaction of intervention with child stunting at 18 months	GEE Coefficient for Stunted at 18 months (95% CI)	p-value	GEE coefficient for Not stunted at 18 months (95% CI)	p-value
		WASH	0.636	N/A		N/A	
	Lean mass index, $Ohms^{-1}$	IYCF	0.058	0.29 (-0.00, 0.58)	0.054	-0.02 (-0.25, 0.20)	0.837
		WASH	0.451	N/A		N/A	
	Impedance Index, m^2 $Ohms^{-1}$	IYCF	0.447	N/A		N/A	
		WASH	0.920	N/A		N/A	
	Phase angle, degrees	IYCF	0.494	N/A		N/A	
		WASH	0.156	N/A		N/A	
	Total skinfold thicknesses, mm	IYCF	0.596	N/A		N/A	
		WASH	0.704	N/A		N/A	
	Peripheral skinfold thickness, mm	IYCF	0.418	N/A		N/A	
		WASH	0.704	N/A		N/A	
	Central skinfold thickness, mm	IYCF	0.993	N/A		N/A	
		WASH	0.854	N/A		N/A	
	Hb, g dl^{-1}	IYCF	0.413	N/A		N/A	
		WASH	0.114	N/A		N/A	

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